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EVIDENCE-BASED PRACTICE

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FPIN
Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

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IN DEPTH

GEMS

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SPOTLIGHT ON PHARMACY

EVIDENCE-BASED PRACTICE

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STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

EDITORIAL POLICY

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DISCLOSURE

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Good vibrations

My father went through a phase where he purchased surplus military vehicles. One of these purchases was a quarter-ton Willys MB jeep that was in the family for years. Drab military green, with blackout lights, power nothing, and no doors, it ran on four cylinders, knob tires and leaf springs. Its ride might have been charitably described as "stiff" but it was, in fact, more like vibratyion-enhanced interrogation. Every pea-sized bit of gravel on the road was transmitted directly up your spine to the base of your skull.[1]

On short rides this was a tolerable nuisance. On two-day rides to remote camp sites in the Mojave Desert, the vibration started to rattle everyone's bones loose. At the weary end of those palavers, it seemed the constant shaking must have damaged *something*. But according to recent research, some folks appear to thrive when they are shaken up a bit.

Researchers performed a meta-analysis of RCTs on something called "whole body vibration exercise" that assessed for effects on bone structure parameters, fractures and falls. They identified 14 RCTs with 1,839 total patients who were predominantly geriatric (mean 74 years old), female (90%), and highly functioning (82% living independently). "Usual activity" was the predominate control. Vibration sessions lasted from 75 seconds to 20 minutes, generally given two or three days a week, and were delivered by devices with names like Vibrosphere®, Vibrafit®, and Power Plate®.

There was no change in the risk of fractures or in bone mineral density at the spine or hip from vibration therapy. However, in three studies of vibration versus usual care that assessed fall rate (N=746), vibration therapy appeared protective (rate ratio 0.67; 95% CI, 0.50–0.89; NNT=17). The evidence was graded as being of moderate quality.

My father sold the jeep many years ago, much to my mother's delight. But now, decades later, they are both frail and have taken a few falls themselves. Given this research, it's not just nostalgia that has me wishing we could take a few more trips together in that unique old rattle trap.

Jon O. Neher

DOI 10.1097/EBP.0000000000002087

Reference

1. Jepsen DB, Thomsen K, Hansen S, et al. Effect of whole body vibration exercise in preventing falls and fractures: a systematic review and meta-analysis. *BMJ Open.* 2017; 7: e018342.

Have you tried eating kiwi? Green kiwifruit for functional constipation

Gearry R, Fukudo S, Barbara G, et al. Consumption of 2 Green Kiwifruits Daily Improves Constipation and Abdominal Comfort-Results of an International Multicenter Randomized Controlled Trial. *Am J Gastroenterol*. 2023; 118(6):1058–1068. doi: 10.14309/ajg.0000000000002124.

DOI 10.1097/EBP.0000000000001966

This multisite prospective single-blind crossover trial in adults with constipation compared two daily green kiwifruits, without the skin, to daily psyllium supplementation containing an equivalent amount of dietary fiber. Patients from New Zealand, Italy, and Japan 18 to 65 years old with minimal comorbidities and uncomplicated functional constipation (FC; n=60), constipation-predominant irritable bowel syndrome (IBS-C; n=61), or no constipation (n=63) received two daily green kiwifruits or 7.5 grams of psyllium supplementation. Most patients (74%) were female. Researchers excluded patients with severe IBS symptoms, gastrointestinal alarm symptoms, elevated C-reactive protein levels, and uncontrolled diabetes. After four weeks of treatment and then a four-week washout period, groups crossed over to the other treatment. In several analyses, the FC and IBS-C groups were considered together as one constipation group. The primary outcome was an increase in weekly complete spontaneous bowel movements (CSBM) compared with baseline. An increase of at least one CSBM per week is clinically significant. Secondary outcomes were patient-reported questionnaires on gastrointestinal symptoms, stool consistency, and quality of life. Study personnel performing data interpretation were blinded to patient groups.

Consumption of two daily green kiwifruits led to an increase in CSBM of 1.7 per week in the IBS-C group ($P=.0003$), 1.5 per week in the functional constipation group ($P<.0001$), and 1.2 per week in healthy patients ($P=.0022$). Psyllium supplementation led to an increase in CSBM of 1.3 per week in the IBS-C group ($P=.0001$) and 1.3 per week in healthy patients ($P=.0022$) but no significant increase in the functional constipation group. No difference was noted between kiwifruit and psyllium in CSBM during any week in any group. Kiwifruit led to improvements in overall symptom scores and constipation-specific scores in all constipated patients. Psyllium led to overall symptom improvement only in the constipation-specific scores in the IBS-C group. Secondary outcomes were mixed in healthy patients. No adverse events were reported with the use of kiwifruit. This study was limited by extensive exclusion criteria and was funded by an international kiwifruit distributor.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**. No additional literature search was conducted.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

Bottom line: Among otherwise healthy adults with uncomplicated constipation disorders, dietary fiber consumption using two green kiwifruit improves bowel habits similar to psyllium supplementation and may better improve constipation-related symptoms. Family physicians can suggest this unique route of fiber consumption for adults with functional constipation or IBS-C.

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Practice Changer

In patients with methamphetamine use disorder and a strong desire to quit, extended-release injectable naltrexone and extended-release bupropion can reduce repeated methamphetamine use in conjunction with standard counseling.

Strength of recommendation: **B**: multicenter, double blind, two-stage, placebo-controlled trial.[1]

Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021; 384(2):140-153. doi:10.1056/NEJMoa2020214.

DOI 10.1097/EBP.0000000000002006

Illustrative case

Jake is a 34-year-old man with long-term methamphetamine use who has decided that he needs to quit drug use to care for his girlfriend and their 2-year-old daughter. He comes to you, stating that he has tried multiple times to quit, and he goes right back because of severe withdrawal symptoms. What might you offer him as possible medication therapy?

Background/introduction

Methamphetamine (meth) is a highly addictive central nervous system stimulant that is associated with a range of health harms. Those harms include psychosis, cardiovascular and renal dysfunction, infectious disease transmission, and overdose.[2] A Morbidity and Mortality Weekly Report by the Centers for Disease Control, using data from the 2015 to 2018 National Surveys on Drug Use and Health (NSDUHs), indicated that the estimated rate of meth use in the past year among adults was 6.6 per 1,000 adults or 1.6 million US adults age ≥18 years old. Among those reporting meth use in the past year, 27.3% reported using meth ≥200 days per year, 52.9% had a meth use disorder, and 22.3% had injected meth.[2]

Amphetamine type stimulants (ATS), with meth being the most frequently used, are a major problem worldwide. In 2017, based on a 2019 report from the United Nations Office on Drugs and Crime, 28.9 million people were using ATS.[3] Meth is the fourth leading cause of overdose deaths in the United States, accounting for 10.6% of deaths in 2016. A cross-sectional study among one million US patients showed a 486.7% increase in meth-positive urine from 2013 to 2019.[3]

A 2020 systematic review looked at 43 studies that enrolled 4,065 participants and evaluated 23 different pharmacotherapies, either alone or in combination, for treating ATS or meth dependence. The most encouraging results were seen in those studies using stimulant agonist treatment (dexamphetamine and methylphenidate), naltrexone and topiramate. Other agents that were found to be somewhat effective, but with less consistency, included bupropion, mirtazapine, riluzole, and pexacerfont. Neither selective serotonin reuptake inhibitors nor tricyclic antidepressants were found to be effective in reducing stimulant use.[4]

Study summary

This multicenter, double-blind, two-stage, placebo-controlled trial (n=403) evaluated the combination of extended-release naltrexone (380 mg intramuscularly every 3 weeks) and extended-release bupropion (450 mg by mouth daily) for efficacy of reducing meth use and safety for adverse events. Study participants included adults 18 to 65 years old meeting DSM criteria for moderate-to-severe amphetamine use disorder criteria with current meth use and opioid negative confirmed by urine drug screens at randomization. Patients were excluded if they were enrolled in current substance use disorder therapy, expected opioid need in the next 90 days (such as a planned surgery), or if they had any contraindications to the study medications, such as a seizure disorder.[1]

In stage 1, 403 participants were randomly assigned in a 1:2.8 ratio to receive naltrexone–bupropion or matching injectable and oral placebo for six weeks. Those in the placebo group who did not respond in stage 1 underwent rerandomization in stage 2 (n=225) and were assigned in a 1:1 ratio to receive naltrexone–bupropion or placebo for another six weeks. All groups were analyzed by intention-to-treat and power analysis for 90% confidence indicated a need for 370 participants.

The primary outcome was meth-negative urine drug screens for three of four screenings at the end of stage 1 and stage 2 or weeks five to six and weeks 11 to 12, respectively. Secondary outcomes included safety outcomes, prevalence of METH-negative urine samples, and changes in meth craving score, PHQ-9 depression score, and scoring on the Treatment Effectiveness Assessment.

The average patient was 41 years old, male (68.7%), White (71.0%) with daily nicotine use (70.6%), and a baseline PHQ-9 score of 20. The weighted response across stages 1 and 2 was 13.6% in the treatment group and

2.5% in the placebo group for a total treatment effect of 11.1% (Wald z-test statistic, 4.53; $P<.001$; NNT=9). Adverse events occurred more frequently in the naltrexone–bupropion group versus placebo and included nausea (32.9% vs 11.3%, $P<.001$), vomiting (11.2% vs 2.4%, $P<.001$), dizziness (10.1% vs 2.7%, $P=.006$), and constipation (9.2% vs 2.4%, $P=.005$). Furthermore, compared with placebo, the weighted naltrexone–bupropion group had statistically higher rates of meth-negative urine samples, larger decreases in METH craving score, larger decreases in PHQ-9 scores, and larger increases in the Treatment Effectiveness Assessment.[1] Adherence was high, and attrition was low in both groups (numbers not provided).

What's new

In patients with meth use disorder and a strong desire to quit, extended-release naltrexone and bupropion can reduce repeated meth use (NNT=9) over a 12-week period in conjunction with standard counseling.[1] This provides objective evidence of efficacious medications to support recovery in patients with meth use disorder, particularly in areas where family physicians do a significant amount of addiction care, such as in rural communities.

Caveats

Of the 1,911 potential candidates who were eligible for screening, only 403 underwent randomization. This was mostly due to patient's unwillingness to adhere to trial protocol. This limits generalizability of study results to only those patients who have a strong desire to quit. In addition, the study only lasted 12 weeks, which does not establish the long-term effect and safety profile of therapy. Translating the treatment into a community practice setting has not been established because the studies were based in an academic medical center setting.

In addition, the authors did not delineate the type of counseling intervention used for all patients, which could also alter reproducibility.

Challenges to implementation

The largest challenge to implementation of this intervention was to identify patients with the desire and willingness to stop meth use, which is highly addictive. In addition, the research was performed in a large academic medical center, and translation to a community-based practice would require significant training of personnel for screening and subsequent monitoring of patients, as well as coordination with community pharmacies to provide treatment medications. Furthermore, the medication cost and administration schedules would need to be considered.

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Are medical abortions performed at home associated with higher rates of complications compared with those performed under supervision in the office?

EVIDENCE-BASED ANSWER

They seem equally effective and safe. Medical abortions with mifepristone administered either in-office or at home followed by misoprostol administered at home do not have an increased risk of surgical completion, side effects, or hospitalization compared with medical abortions performed under office supervision (SOR: **B**, meta-analysis of randomized clinical trials (RCTs) and cohort studies and subsequent RCT and cohort study).

DOI 10.1097/EBP.0000000000001974

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systematic review found 16 prospective cohort studies and three randomized clinical trials (RCTs) (N=11,576) comparing home-based versus clinic-based medical abortions performed up to nine weeks' gestation.[1] All three RCTs and 14 of the cohort studies were from settings deemed low-to-middle resource (Albania, Bangladesh, China, India, Nepal, Nigeria, Tunisia, Turkey, and Vietnam) while two cohort studies were from France, a high-resource setting. Patients had mean ages ranging from 24.3 to 32.2 years old. All studies used 200 mg of provider-administered PO mifepristone followed by 400 to 800 μg of PO, buccal, vaginal (PV), or sublingual (SL) misoprostol. The intervention groups self-administered the misoprostol, whereas the comparison groups received misoprostol from a provider at a health care facility. The primary outcome was successful abortion measured by complete uterine evacuation without the need for surgical intervention, and secondary outcomes were side effects (pain/cramps, vomiting, fever/chills, nausea, heavy bleeding) and complications requiring hospitalization. Pooled data from the three RCTs (N=1,452; RR 0.99, CI 0.98–1.01) and 16 cohort studies (N=10,124; RR 0.99, CI 0.97–1.01) found no difference in rates of successful abortion between intervention and comparison groups and no differences in rates of side effects or complications requiring hospitalization, although studies inconsistently reported these outcomes. The review graded the evidence quality as moderate for the three RCTs and very low for the 16 cohort studies because of high risk of bias.

A 2022 noninferiority RCT (n=692) from South Africa investigated the effectiveness and safety of a telemedicine protocol for medical abortion compared with standard care.[2] Patients were on average 28 (range 24–33) years old at 6.8 (range 6–7.8) weeks' gestation; 47% reported food scarcity, and 29% lived in shack-type housing. Telemedicine patients were counseled and given instructions through a smartphone app and subsequently picked up 200 mg PO mifepristone and 800 μg SL misoprostol (administered 24–48 h after mifepristone) to take at home. Standard care patients received all counseling and instructions in person, completed an ultrasound (US) in office to confirm intrauterine pregnancy and dating, and took 200 mg PO mifepristone in the office with directions to take 800 μg SL misoprostol at home 24 to 48 h later. A registered nurse palpated the uterus of all telemedicine patients at medication pick up, and they received a dating US if they had inconsistent size for date of gestation or there was no uterus palpable. In addition, telemedicine patients with a previous tubal ligation or history or symptoms of ectopic pregnancy had an US at medication pick up and were excluded from the study if they had an ectopic pregnancy. The primary outcome was complete abortion, defined as terminated pregnancy without the need for additional medical or surgical management after initial treatment. Secondary outcomes included measures of safety—emergency clinical visits, blood transfusion, and hospitalization within two days of misoprostol ingestion. Both primary and secondary outcomes were assessed at five days and six weeks after medical abortion. In an intention-to-treat analysis, both telemedicine and standard care patients had successful rates of complete abortion (95.6% vs 96.6%, respectively), and the rate difference (–1.1%; 95% CI, –4%

to 1.7%) was within the noninferiority margin; furthermore, there were no statistically significant differences in emergency care visits, blood transfusions, or hospital admissions between groups.

A 2021 retrospective cohort study (n=52,142) evaluated whether medical abortions performed through telemedicine without a previous pregnancy test or US were equally effective and safe compared with those performed in the office.[3] The study population included patients who accessed early medical abortion at the three largest abortion providers in the United Kingdom (UK) over six months encompassing a service model change during the COVID-19 pandemic. Before March 2020, all patients seeking abortion in the United Kingdom were required to attend in-person appointments to receive an US and have 200 mg PO mifepristone administered in the clinic followed 24 to 48 h later by 800 μg buccal, SL, or PV misoprostol taken at home. By March 30th, 2020, governments in the United Kingdom had issued emergency orders allowing abortion providers to prescribe in-home use of mifepristone and misoprostol up to 10 weeks' gestation through telemedicine without preprocedure pregnancy testing or US. Abortion providers required an in-person evaluation for patients deemed high risk for ectopic pregnancy or with a pregnancy greater than 10 weeks' gestation by last menstrual period. The intervention cohort included 18,435 patients (61%) who received a no-test telemedicine assessment and 11,549 (39%) who were seen in-person between April 6 and June 30, 2020. The traditional cohort was defined as those who had an early medical abortion between January 1 and March 1, 2020. Patients in the intervention cohort were slightly older (mean 28.5 vs 27.8 years old; $P<.001$), more likely multiparous (60.8% vs 54.3%; $P<.001$), and had more previous abortions (mean 44.28% vs 40.9% $P<.001$) compared with the traditional cohort. There were no statistically significant differences between the intervention versus traditional cohorts regarding treatment success (98.8% vs 98.2%), number of serious adverse events (0.02% vs 0.04%), or incidence of ectopic pregnancy (0.2% vs 0.2%). Limitations included the reliance on electronic medical record data and inability to actively follow-up patients after abortions. EBP

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The authors declare no conflicts of interest.

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Addressing disparities in access to Opioid Use Disorder medications based on race

Racial inequality in receipt of medications for opioid use disorder

Barnett ML, Meara E, Lewinson T, et al. Racial Inequality in Receipt of Medications for Opioid Use Disorder. N Engl J Med. 2023; 388(19):1779-1789. doi:10.1056/NEJMsa2212412 DOI 10.1097/EBP.0000000000002011

KEY TAKEAWAY: Black patients received less medications to treat OUD when compared with White patients

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BACKGROUND: Opioid use disorder (OUD) is prevalent in the United States, and Black people face inequities in receiving medication to treat the disorder when compared with other races. Black patients had the largest increase from 2010 to 2020 in opioid overdose mortality of all groups. However, evidence suggests they were less likely to receive medications to treat OUD.

PATIENTS: Black, Hispanic, and White patients who had OUD events
INTERVENTION: Treatment of OUD
CONTROL: No treatment for OUD
OUTCOME: Receipt of buprenorphine, naloxone, and naltrexone for treatment of OUD

METHODS BRIEF DESCRIPTION:

- Medicare claims from 2016 to 2019 for Black, Hispanic, and White patients with OUD based on an index event were used.
- 40% of these claims were randomly selected.
- Index events included nonfatal opioid overdoses treated in the ED or inpatient setting; hospitalizations with an injection drug use–related infection; or inpatient, residential rehab, or detox care with a primary diagnosis of OUD or an OUD diagnosis in the last 30 days.
- The utilization rates of buprenorphine, naloxone, naltrexone, opioid analgesics, and benzodiazepines to treat OUD were compared in Black, Hispanic, and White patients.
- Outcomes were measured by identifying OUD-related index events among Black, Hispanic, and White patients and recording the number of patients from each race receiving buprenorphine, naloxone, naltrexone, opioid analgesics, and benzodiazepines in the 180 days after the index event.
- 23,370 beneficiaries were included.
  Black=3,524
  Hispanic=1,858
  White=17,988
- Total of 25,904 OUD events

INTERVENTION (# IN THE GROUP): N/A
COMPARISON (# IN THE GROUP): N/A
FOLLOW-UP PERIOD: 2016-2019

RESULTS:
Primary outcomes:

- Black patients received less buprenorphine compared with White and Hispanic patients: 13% Black patients, 19% of Hispanic patients, and 23% of White patients.
  - The Black versus White mean difference [MD] –8.7% (95% CI, –11 to –6.0)
  - Hispanic versus White MD –4.2% (95% CI, –6.7 to –1.8)
  - Hispanic versus Black MD 4.4% (95% CI, 2.0–6.9)
- Black patients received less naloxone compared with White and Hispanic patients: 14% Black patients, 21% Hispanic patients, and 23% White patients.
  - The Black versus White MD –6.7% (95% CI, –9.5 to –3.7)
  - Hispanic versus White MD –2.3% (95% CI, –5.1 to 0.5)
  - Hispanic versus Black MD 4.3 (95% CI, 1.5–7.1)

LIMITATIONS:

- The study of Medicare fee-for-service beneficiaries with disability may not be generalizable to other groups. Beneficiaries with disability represent a disproportionate share of persons with opioid-related overdose in the United States.
- The likelihood of a written prescription being filled may differ according to race or ethnic group.
- Diagnostic coding of OUD may vary according to racial or ethnic group. EBP

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HIV and COVID-19 virus: A real cross-reactivity or just a simple coincidence?

Increase in False Positive Fourth Generation HIV Tests in Patients with COVID-19 Disease

Gudipati S, Shallal A, Peterson E, Cook B, Markowitz N. Increase in False Positive Fourth Generation HIV Tests in Patients with COVID-19 Disease [published online ahead of print, 2023 May 9]. *Clin Infect Dis*. 2023; ciad264. doi:10.1093/cid/ciad264 DOI 10.1097/EBP.0000000000002042

KEY TAKEAWAY: Patients with active PCR COVID-19 are more likely to have a false-positive (FP) fourth-generation HIV test.

STUDY DESIGN: Retrospective, cross-sectional study

LEVEL OF EVIDENCE: STEP 3

BACKGROUND: During the first severe acute respiratory syndrome pandemic in 2003, it was found that HIV and SARS-CoV-1 viral proteins had similar structures, suggesting a potential for immune system cross-reactivity. This analysis assessed whether this is also true of SARS-CoV-2 viral proteins.

PATIENTS: SARS-CoV-2 (COVID-19) positive patients
INTERVENTION: HIV testing
CONTROL: Not applicable
OUTCOME: False-positive HIV tests

METHODS BRIEF DESCRIPTION:

- Patients with PCR COVID-19 testing that resulted within two weeks of an HIV fourth-generation assay were included.
- HIV screening was performed with a fourth-generation HIV Ag/Ab test in accordance with Centers for Disease Control and Prevention guidelines.
- Presence or absence of SARS-CoV-2 infection was determined by real-time PCR testing for SARS-CoV-2 viral RNA from nasopharyngeal with commercial PCR systems validated for clinical use under emergency authorization.

INTERVENTION (# IN THE GROUP): 31,910 patients with a COVID-19–positive PCR test and HIV test.
COMPARISON (# IN THE GROUP): Not applicable
FOLLOW UP PERIOD: Not applicable

RESULTS:

- Patients with active COVID-19 were significantly more likely to have a false-positive fourth-generation HIV test (OR 2.9; 95% CI, 1.4–5.9).

LIMITATIONS:

- The article does not mention if any of the 87 false-positive patients had any history of rheumatology disease or other diseases that could have caused a cross-reaction with the antibodies of the HIV test.
- Cofounder bias.
- No description of the type of COVID-19 variants circulating.

EBP

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Is insulin icodec, a once-weekly basal insulin, replacing daily basal insulin?

Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (onwards 2): a phase 3a, randomized, open label, multicenter, treat-to-target trial

Philis-Tsimikas A, Asong M, Franek E, et al. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomized, open label, multicenter, treat-to-target trial [published correction appears in Lancet Diabetes Endocrinol. 2023 May 29]. *Lancet Diabetes Endocrinol*. 2023; 11(6):414-425. doi:10.1016/S2213-8587(2300093-1)
DOI 10.1097/EBP.0000000000002012

KEY TAKEAWAY: Insulin icodec, a once-weekly basal insulin, is just as effective, if not slightly more effective, at reducing HbA1c when compared with insulin degludec in patients with type 2 diabetes.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BACKGROUND: Patients with type 2 diabetes taking a once-daily basal insulin have issues with patient compliance because of the number of injections needed a year, which in return may lead to a lower glycemic control. A newer insulin called icodec is a once-weekly basal insulin that would significantly reduce the number of injections within a year. There are studies comparing icodec with other daily basal insulins and showing equal efficacy in HbA1c reduction. Early studies have shown icodec has a similar safety profile as normal basal insulins.

PATIENTS: Adults with type 2 insulin-dependent diabetes
INTERVENTION: Insulin icodec (weekly)
CONTROL: Insulin degludec (daily)

OUTCOME: HbA1C reduction (primary outcome) and weight gain (secondary outcome)

METHODS BRIEF DESCRIPTION:
- Open-label trial to both researcher and participants.
- Patients with type 2 insulin-dependent diabetes who were uncontrolled (HbA1c 7–10%) on a once-daily or twice-daily basal insulin.
- Randomized 1:1 with insulin icodec or insulin degludec.
- Patient's HbA1c, body weight, and hypoglycemic events were recorded over a period of 26 weeks.
- The primary outcome was a reduction in HbA1C.

INTERVENTION (# IN THE GROUP): 256
COMPARISON (# IN THE GROUP): 253
FOLLOW UP PERIOD: 26 weeks

RESULTS:
Primary outcome:
- Insulin icodec had a higher reduction of HbA1c compared with insulin degludec.
  - Mean HbA1c: 7.2% icodec versus 7.42% degludec
  - Average change in HbA1c –0.93% icodec and –0.071 degludec, mean difference –0.22%; 95% CI –0.37 to –0.08.
  - Further statistical analysis established superiority of icodec versus degludec ($P=.0028$)

Secondary outcomes:
- Insulin icodec resulted in an increase in body weight by an average of 1.7 kg when compared with degludec.
  - 1.40 kg versus -0.30 kg; mean difference 1.7 kg; 95% CI 0.76 to 2.63
- No statistically difference between clinically significant (blood sugar <54 mg/dL) or severe hypoglycemia (associated cognitive impairment) for icodec when compared with degludec

LIMITATIONS:
- Open-label trail
- Treatment adherence was not assessed

EBP

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The author declares no conflicts of interest.

Intrapartum azithromycin for planned vaginal delivery: improving maternal mortality

Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth

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KEY TAKEAWAY: In low- and middle-income countries, a single intrapartum dose of oral azithromycin reduced maternal morbidity and mortality in planned vaginal births.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFO: Peripartum infections are one of the top three causes of maternal death worldwide. Previous studies have shown lower incidence of infection in pregnant patients undergoing cesarean delivery who also received a single prophylactic dose of azithromycin. Few studies have analyzed whether prophylactic azithromycin has a similar effect in reducing infection risk in pregnant patients undergoing a vaginal delivery.

PATIENTS: Pregnant patients in low- and middle-income countries
INTERVENTION: Azithromycin 2,000 mg orally
CONTROL: Placebo
OUTCOME: Sepsis or death of the delivering patient, stillbirth, neonatal sepsis, or death

SECONDARY OUTCOMES: Medication side effects and/or allergy, development of any infection, therapeutic use of antibiotics, hospital readmission, unscheduled healthcare visits

METHODS BRIEF DESCRIPTION:

- The study was conducted at eight hospitals in seven low- or middle-income countries in Africa and Asia.
- Patients were included in the study if they were ≥28 weeks' gestation and were admitted for early labor or planned induction of labor.
- Patients were excluded if they had any of the following: pre-existing infection that required antibiotics, heart disease or arrhythmia, an azithromycin or macrolide allergy, use of azithromycin or other macrolides in the prior three days, planned cesarean delivery, active labor (greater than 6 cm dilated), or any other medical condition that was considered a contraindication by the investigators.
- A single dose of 2 g of oral azithromycin (given as 4 500 mg pills) was administered directly after randomization.
- Research staff administered the medication and directly observed pill consumption.
- Sepsis in the delivering patient was defined as fever (greater than 100.4F or 38C) or hypothermia (less than 96.8F or 36C) plus one or more of the following: tachycardia (≥120 beats per minute), hypotension, tachypnea (>24 breaths per min), altered mental status, decreased urine output (<500 mL over 24 hours), jaundice, or renal failure (creatinine >1.2 mg/dL)
- Neonatal sepsis was defined as the presence of any of the following: fever, hypothermia (<95.9F or 35.5C), severe chest retractions, hypotonia or movement only on stimulation, poor or no feeding, convulsions, pneumonia, or meningitis.
- Patients were instructed on signs/symptoms of infection and were told to contact the research team or go to the nearest healthcare facility with any issues.
- Outcomes were obtained through medical records or directly from patients before discharge and during visits at postpartum days 3, 7, 14, 28, and 42.

INTERVENTION (# IN THE GROUP): 14,590
COMPARISON (# IN THE GROUP): 14,688
FOLLOW-UP PERIOD: 42 days

RESULTS:
Primary Outcome:

- The treatment group had a significant reduction in death or sepsis of the delivering patient when compared with the control group (1.6% vs 2.4%; adjusted RR 0.67; 95% CI 0.56–0.79).

- The incidence of sepsis in the delivering patient alone was less in the treatment group when compared with the control group (1.5% vs 2.3%; relative risk 0.65; 95% CI, 0.55–0.77).
- No significant difference was observed in the incidence of delivering patient death from any cause between the two groups.
- No significant difference was observed in neonatal stillbirth, death, or sepsis between the two groups.

Secondary Outcome:

- The treatment group had relative risk (RR) reductions of the following maternal infections:
  - ○ Endometritis (RR 0.66; 95% CI, 0.55–0.79)
  - ○ Perineal wound infection (RR 0.80; 95% CI, 0.65–0.99)
  - ○ Cesarean wound infections (RR 0.57; 95% CI, 0.43–0.75)
  - ○ Pyelonephritis (RR 0.26; 95% CI, 0.13–0.50).
  - ○ No difference was observed in the rate of abdominal or pelvic abscess, mastitis, breast abscess, pneumonia, or other bacterial infections.
- The treatment group had decreased rates of maternal readmission ≤42 days postpartum (RR 0.65; 95% CI, 0.52–0.82) and unscheduled postpartum visits (RR 0.79: 95% CI, 0.73–0.84).
- No statistical difference in neonatal infections, readmission rates ≤42 days old, or unscheduled visits.
- No significant difference was observed between the groups in reported medication side effects (nausea, vomiting, diarrhea).

LIMITATIONS:

Maternal mortality rates (MMR) expressed as maternal deaths per 100,000 live births are significantly higher in the studied countries than in the United States, although the proportion of maternal mortality due to infection is similar.

The incidence of maternal sepsis was lower than expected, and the rate of prophylactic use of antibiotics was higher in the Asian sites, which may blunt statistical significance.

Azithromycin covers for atypical organisms (ureaplasmas, mycoplasmas) that were not able to be cultured. More research is needed to identify whether asymptomatic carriers should be treated before vaginal delivery.

Routine azithromycin use may increase antibiotic resistance. EBP

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In patients with plantar fasciitis, do corticosteroid injections provide equal or greater pain relief outcomes compared with alternative treatment options?

EVIDENCE-BASED ANSWER

The use of local corticosteroid injections in patients with plantar fasciitis may lead to some short-term benefit compared with placebo, but the benefit seems marginal at best (SOR: **A**, systematic reviews with meta-analysis of mostly randomized controlled trials [RCTs]). Corticosteroid injections do not demonstrate superiority to any other common treatments for plantar fasciitis (SOR: **A**, systematic review with network meta-analysis of mostly RCTs).

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This clinical question was developed as an HDA through a standardized systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 systematic review of 36 randomized controlled trials (RCTs) and three quasi-RCTs (N=2,492) included 18 treatment comparisons in adults who reported plantar fasciitis heel pain.[1] Corticosteroid injections were combined with local anesthetic agents in 34 of the trials. Five trails (N=350 patients) found less heel pain in short-term follow-up (less than 1 month) in the corticosteroid injection groups versus placebo or no treatment groups using a 0–100 point visual analogue scale (VAS) scores (mean difference [MD] –6.4; 95% CI, –11.1 to –1.6]; I^2=65%; "low quality" evidence per GRADE criteria). It should be noted that the minimal clinically important difference (MCID) for average heel pain is eight, casting doubt on any recognizable clinical benefit. In addition, when the short-term data were limited to the three placebo-controlled RCTs (N=256), the potential benefit was further diminished (MD –4.2; 95% CI, –9.4 to 1.0). When assessing longer-term follow-up at one to six months, six trials (N=382) found no difference in heel pain on the 0–100 VAS between treatment and placebo groups (MD –3.5; 95% CI, –8.4 to 1.5; I^2=40%; "low-quality" evidence per GRADE criteria). Four trials (N=219) with follow-up periods of one to 18 months found no serious adverse events such as plantar fascia rupture or injection site infection, although the quality of this evidence was assessed to be "very low" per GRADE criteria.

A network meta-analysis from 2019 with 41 studies (N=2,889) compared corticosteroid injections and seven other treatments for plantar fasciitis in adults, including injections of autologous whole blood, platelet-rich plasma, and botulinum toxin A, as well as dry needling, ultrasound therapy, extracorporeal shock wave therapy, and oral NSAIDs.[2] Of the studies including corticosteroid injections as a comparison (N=1,035), 15 were double-blinded RCTs, three were single-blinded RCTs, one was an open-label study, and one was of an unspecified design. A 0–10 point VAS was used to assess improvement in pain at one, two, three, and six months. A significant difference in VAS scores was found for corticosteroid injections compared with placebo at one month (MD –1.7; 95% CI, –3.2 to –0.22) and at three months (MD –2.1; 95% CI, –4.1 to –0.17), but not at two and six months, and also not when compared with any other interventions in the network meta-analysis. The MCID for the 10-point VAS being approximately 0.8 suggests again that the differences noted compared with placebo at one and three months may be statistically significant but not necessarily clinically so. EBP

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Are oral antifungals more effective than intravaginal antifungals at treating women with uncomplicated vulvovaginal candidiasis?

EVIDENCE-BASED ANSWER

There is no significant difference between the clinical cure rate of uncomplicated vulvovaginal candidiasis at 1- to 12-week follow-up in women treated with oral versus intravaginal antifungals (SOR: **A**, systematic review of randomized, controlled trials [RCTs]). The mycological cure rate of vulvovaginal candidiasis is slightly greater after treatment with oral antifungals compared with intravaginal antifungals, with a number needed to treat of 33 at one- to two-week follow-up and 17 at 2- to 12-week follow-up (SOR: **C**, systematic review of RCTs using disease-oriented evidence). Guidelines show no preference for oral or intravaginal antifungals (SOR: **C**, consensus and evidence-based guidelines).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systematic review and meta-analysis of 26 RCTs (N=5,007) assessed the relative effectiveness of oral versus intravaginal antifungal treatment options for uncomplicated vulvovaginal candidiasis.[1] The review included trials conducted in a variety of regions, including Europe, Asia, Africa, and the United States. Patients were women aged 16 to 65 years with uncomplicated vulvovaginal candidiasis (diagnosed by positive culture and/or microscopy for yeast). Trials compared treatment with oral antifungals (fluconazole or itraconazole) with multiple intravaginal azole antifungals. Treatment doses and durations varied. For oral antifungals, the most common treatment studied was a single dose of fluconazole 150 mg (20 trials), but six trials used multiple doses of fluconazole (50–200 mg) or itraconazole (200–400 mg) for up to three days. For intravaginal azoles, clotrimazole was the most common medication used (18 trials), but trials included six other topical agents (butoconazole, econazole, fenticonazole, miconazole, sertaconozole, and terconazole) and treatments varied from a single dose to seven daily doses. The primary outcome was the clinical cure of infection at short-term (5–15 days) and long-term (2–12 weeks) follow-up. Secondary outcomes included mycological cure rates and side effects. Moderate-certainty evidence showed no difference in the clinical cure of vulvovaginal candidiasis between those treated with oral versus intravaginal antifungals at short-term (13 trials, N=1,859; odds ratio [OR] 1.1; 95% CI, 0.91–1.4) and long-term (9 trials, N=1,042; OR 1.1; 95% CI, 0.77–1.5) follow-up; however, mycological cure was slightly greater after treatment with oral compared with intravaginal antifungals at short-term (19 trials, N=3,057; 83% vs 80%; OR 1.2; 95% CI, 1.0–1.5; number needed to treat [NNT]=33) and long-term (13 trials, N=1,661; 72% vs 66%; OR 1.3; CI, 95% 1.1–1.6; NNT=17) follow-up. There did not seem to be a significant difference in side-effect rates between the two treatment groups; however, the authors noted that the level of evidence was low and, therefore, uncertain. Side effects for intravaginal treatment were primarily associated with local reactions, whereas oral treatment side effects were more often associated with systemic symptoms, such as gastrointestinal symptoms and headaches. Key potential sources of bias included lack of blinding for patients taking oral versus vaginal treatments (only 2 trials attempted to blind route of administration) and noncompliance with treatment regimen (only 6 trials reported compliance checks).

The Infectious Diseases Society of America published a clinical practice guideline in 2016 for the management of candidiasis infections.[2] For uncomplicated vulvovaginal candidiasis, topical and oral antifungals were noted to produce equivalent results (based on one systematic review, strong recommendation, high-quality evidence). Panel members reported multiple conflicts of interest, which were reviewed by three external peer reviewers, but the effects of these conflicts were unclear.

The Centers for Disease Control and Prevention released a guideline for sexually transmitted diseases in 2021 that included a section on treatment options for vulvovaginal candidiasis based on a systematic literature review and expert opinion.[3] This guideline listed topical and oral agents for treatment of uncomplicated vulvovaginal candidiasis without preference for either one (no strength of recommendation or evidence grade provided).

The 2020 American College of Obstetricians and Gynecologists practice bulletin on vaginitis in nonpregnant patients recommended either single-dose oral fluconazole or intravaginal azole therapy for the treatment of uncomplicated vulvovaginal candidiasis (level C recommendation based primarily on consensus and expert opinion).[4] The guideline noted that the treatment choice should be based on factors such as patient preference, cost, convenience, adherence, ease of use, and history of response or adverse reactions to previous therapies. EBP

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Does supplementation with vitamin D reduce the severity of symptoms in premenopausal women with premenstrual syndrome?

EVIDENCE-BASED ANSWER

Vitamin D supplementation may be associated with a decrease in symptoms of premenstrual syndrome (PMS) but is more likely to improve symptoms in women with pre-existing hypovitaminosis D (SOR: **C**, inconsistent, small randomized controlled trials).

DOI 10.1097/EBP.0000000000001972

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 systematic review and meta-analysis analyzed five interventional and 11 observational studies (N=4,946) to determine the relationship between vitamin D and premenstrual syndrome in different ethnic and geographical populations of premenopausal women.[1] Of five interventional studies, three looked specifically at the role of vitamin D alone in premenstrual syndrome. In one randomized controlled trial (RCT), 86 women 15 to 45 years old who met the American Psychiatric Association criteria for PMS were asked to fill out a standardized daily symptom report (DSR) for two months. The DSR is a questionnaire in which patients rate the severity of 17 PMS symptoms on a scale of zero to three (maximum score 51). Patients were then given oral supplementation with vitamin D (200 mg daily for 2 months), vitamin E, or a placebo. Patients had a decrease in average PMS scores after treatment with vitamin D (37 vs 26, $P<.0001$); however when compared with placebo, there was no difference ($P>.05$). One RCT studied 158 girls and women 15 to 21 years old who had psychiatric and cognitive PMS symptoms as well as hypovitaminosis D, with vitamin D levels less than or equal to 10 ng/mL. The women in the treatment arm were given an initial dose of 200,000 IU orally, followed by 25,000 IU oral vitamin D every two weeks for four months. Patients were excluded from the study if they had any concurrent psychiatric diagnosis. Symptoms were measured by patient report using the PMS Daily Symptom Report, which evaluates 17 symptoms of PMS. At the end of the treatment period, women who received vitamin D had less anxiety (50 vs 21, $P<.001$), irritability (130 vs 70, $P<.001$), crying (41 vs 30, $P<.001$), and disturbed relationships (150 vs 70, $P<.001$) than patients who received placebo. A third, quasiexperimental study evaluated the effects of vitamin D supplementation on PMS and dysmenorrhea by placing 897 girls 12 to 18 years old into four treatment groups based on diagnoses: PMS, dysmenorrhea,

PMS and dysmenorrhea, and control. These patients were treated with 50,000 IU of oral vitamin D weekly for nine weeks. At the end of the treatment period, there was a decrease in PMS prevalence when compared with placebo (14.9% vs 4.8%, $P<.001$). A meta-analysis of seven observational studies (N=1,344) showed no association between vitamin D supplementation and premenstrual syndrome.

A 2019 randomized control trial studied the effect of vitamin D supplementation on PMS symptoms in the treatment of 130 women 18 to 30 years old with hypovitaminosis D, with vitamin D level less than 20 ng/mL.[2] Women were diagnosed with PMS based on premenstrual symptoms screening tool and based on diagnostic criteria of the American College of Obstetrics and Gynecology. Women were excluded from the study if they had any chronic or mental diseases or if they were taking vitamin D or any nutrient supplement, laxative, or hormone medication. Women were treated for three months with either 2,000 IU every other day of oral vitamin D or placebo. PMS symptoms in patients taking vitamin D were not statistically different from those taking placebo, although both groups improved over baseline. Limitations to this study included a short duration of treatment and inclusion criteria specific to women with vitamin D deficiency.

A 2019 randomized control trial studied the effect of vitamin D supplementation on inflammatory and antioxidant markers in 38 women 18 to 25 years old with hypovitaminosis D (vitamin D level less than or equal to 10 ng/mL), who were diagnosed with PMS based on a PMS Daily Symptoms Rating form (scale not well described), using the diagnostic criteria of the American Psychiatry Association.[3] In addition, IL-10, IL-12, and total antioxidant capacity (TAC) were measured in both the treatment and control groups before and after treatment. Inclusion criteria were single women with normal BMI, regular menstrual cycles, no chronic illness, and no contraceptive, anti-inflammatory, antipsychotic, or vitamin D use. Women in the treatment group were given 50,000 IU of oral vitamin D every two weeks for four months. Patients in the intervention group had improvement in PMS symptoms when compared with the placebo group (-18 vs -7; $P<.001$). In addition, levels of both IL-10 and IL-12 decreased after intervention compared with placebo and TAC increased after intervention. EBP

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Do intra-articular stem cell injections improve pain and function in patients with osteoarthritis of the knee?

EVIDENCE-BASED ANSWER

Mesenchymal stem cell intra-articular injections reduce pain and improve motor function in patients with knee osteoarthritis (OA) in the short term compared with controls (SOR: **A**, meta-analyses of randomized controlled trials [RCTs]). Intra-articular injection of autologous adipose-derived stem cells or adipose-derived stromal vascular fractions without adjuvant therapy for patients with knee OA also show good clinical efficacy and safety. (SOR: **A**, meta-analysis of RCTs).

DOI 10.1097/EBP.0000000000001980

This clinical question was developed as a HDA through a standardized systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systemic review and meta-analysis of 10 randomized controlled trials (RCT's) (n=335) compared the effectiveness of hyaluronic acid, placebo, or conservative management with stem cell injections for knee osteoarthritis. Four studies used bone marrow mesenchymal stem cell (MSC), four used adipose-derived MSC, and placental or umbilical derived stem cells were used in two. Controls for studies included hyaluronic acid (HA) in five, placebo in four, and conservative management (simple analgesia, exercise/weight management program, biomechanical adjustment with bracing or orthotics) in one. Outcomes included changes in 0 to 100 visual analog scale (VAS) pain scores, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, a 24-item self-administered questionnaire with subscales for pain, stiffness, and physical function (higher scores indicate worse symptoms), and cartilage volume measured by MRI using Noyes grading system. VAS scores were assessed in 7 studies. Follow-up ranged from six months (3 studies) to 12 months (3studies).[1] Compared with control groups, VAS scores of MSC groups decreased (mean difference [MD] –19.2; 95% CI, –26.3 to –12.2; $P<.00001$). Seven studies assessed WOMAC scores at baseline and follow-up, one at six months and the others at 12 months. Compared with placebo, WOMAC scores in MSC groups significantly improved: total scores (standardized mean difference [SMD] –0.66; 95% CI, –1.09 to –0.23; $P=.003$), pain scores (SMD –0.46; 95% CI, –0.74 to –0.17; $P=.002$), stiffness scores (SMD –0.32; 95% CI, –0.64 to 0.00; $P=.05$), and functional scores (SMD 0.36; 95% CI, –0.69 to –0.04; $P=.03$). Assessment of MRI results using changes in cartilage volume in 3 studies showed that cartilage volume in the MSC group moderately increased (SMD 0.69; 95% CI: 0.25–1.13, $P=.002$). One study was classified as high-risk reporting bias due to the lack of original data, and two studies were at risk for attrition bias due to incomplete data on overall WOMAC scores and subscales.

A 2021 systemic review and meta-analysis of nine RCTs (N=406) compared MSC with control group WOMAC and VAS scores in patients with knee osteoarthritis assessing degree of cartilage repair and pain-related scores. Inclusion criteria were RCT study, HA control, and intra-articular stem cells injected into patients with knee osteoarthritis (OA). Four studies used injected bone marrow mesenchymal stem cells (BMSCs), two used umbilical cord MSCs, two used peripheral blood stem cells and one used adipose derived stem cells.[2] Hyaluronic acid (HA) injection was used as the control. Follow-up ranged from six and 12 months. VAS pain scores improved moderately compared with controls (SMD –0.68; 95% CI, –1.06 to –0.30; $P=.0005$). Both WOMAC-total and WOMAC-pain were reduced significantly (SMD –0.49; 95% CI, –0.90 to –0.07; $P=.02$ and SMD –0.51; 95% CI, –0.89 to –0.13; $P=.008$, respectively). Limiting factors include small number of studies and lack of uniformity of stem cell concentration and type.

A 2022 meta-analysis of five RCTs evaluated the effectiveness of intra-articular injections of adipose-derived stem cells (ASCs) or adipose-derived stromal vascular fractions (ADSVF's) in 177 knees with OA. Three studies compared ASC treatment with placebo and no injection, and two compared ADSVF versus placebo and HA. OA was graded using the Kellgren–Lawrence grading scale and knee alignment. Inclusion criteria included unilateral OA, less than 5 degrees varus or valgus alignment, and failure of at least two conservative treatments. Key outcomes included pain scores, total WOMAC functional change, cartilage structural changes on MRI, and safety. Follow-up was at six and 12 months. Total mean improvement in 100-mm VAS scores was higher in treatment groups versus controls (SMD 1.06; 95% CI, 1.19–2.02; $P<.0001$) in 4 studies. Subgroup analysis for study groups showed larger VAS improvements in the ASC (SMD 1.32; 95% CI, 0.88–1.76; $P<.0001$) and ADSVF (SMD 3.64; 95% CI, 2.47–4.82; $P<.0001$) versus controls.[3] Total WOMAC scores at six months in 4 studies showed symptom improvement in study groups versus controls (SMD 0.75; 95% CI, 0.39–1.11; $P<.0001$). MRI assessment of cartilage and structural changes in 3 studies found that the treatment groups had better changes in cartilage status versus controls. ASC and ADSVF showed similar efficacy, and no serious adverse events were reported. Quantitative analysis of MRI findings was not performed due to heterogeneity of MRI modalities. No study was assessed as excellent quality, three were good quality, and two fair quality. Limiting factors include small number of studies and lack of uniformity of MRI imaging modalities for the evaluation of cartilage change. EBP

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In pregnant women with opioid use disorder managed with buprenorphine, does discontinuing buprenorphine before labor improve peripartum pain management?

EVIDENCE-BASED ANSWER

Buprenorphine should be continued in the peripartum period for pregnant women with opiate use disorder because adequate pain control can be achieved in these patients when maintained on buprenorphine (SOR: **B**, small cohort studies). Discontinuing buprenorphine in these women may lead to poor acute pain control and additional risks for both mother and child including relapse to illicit substance use and neonatal abstinence syndrome.

DOI 10.1097/EBP.0000000000001989

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2019 systematic review of five cohort studies and seven case series and care reports (N=456) investigated pain control in continuation or discontinuation of buprenorphine before a medical procedure in patients with opiate use disorder (OUD).[1] Procedures included, but were not limited to, vaginal and cesarean deliveries, and OUD was defined as a maladaptive use of opioids, leading to addiction and emotional impairment. A subgroup of three cohort studies and two case studies (N=393) with a specific focus on peripartum pain control was identified and is summarized below. Buprenorphine dosing ranged from 8.0 to 16.9 mg. Control subjects received opiates per institution protocol. Data could not be pooled and only one study reported quantitative data. In a 2010 retrospective cohort study, pain control was compared in pregnant women with OUD managed with buprenorphine (n=63) with a matched control group. The primary outcome was opioid consumption in the postpartum period measured in morphine milligram equivalents, and the secondary outcomes were visual analogue scale (VAS) pain scores ranging from 0 to 10 and intrapartum opioid consumption. The cohort group was further divided into women who underwent cesarean section (n=19) and those who delivered vaginally (n=44). For vaginal deliveries, opioid utilization in the postpartum period was not statistically higher in the buprenorphine group compared with the control group (11.8 vs 5.4 mg/24 hours; P=.10); however, these same women in the buprenorphine group did have significantly higher VAS pain scores (2.7 vs 2.1, P=.006). After cesarean delivery, women on buprenorphine had significantly higher pain scores (5.1 vs 3.3, P=.009) and opioid utilization (89.3 vs 60.9 mg/24 hours; P=.004) in the postpartum period than the women in the control group. The other four studies in this subgroup were only reported qualitatively and had similar findings demonstrating that adequate pain control was obtained in women who underwent vaginal or cesarean delivery and continued on buprenorphine throughout the peripartum period. The authors of this review cautioned against discontinuing buprenorphine in the peripartum period because abrupt discontinuation would require withdrawal prevention with short-acting opioids and might serve as a trigger for relapse.

A 2022 matched cohort study (n=92) compared the effectiveness of pain control in pregnant women with OUD who were continued on buprenorphine to a matched cohort of similar pregnant women.[2] Both groups underwent cesarean delivery, and pregnant women taking buprenorphine were stratified into groups based on their prehospital dose of buprenorphine defined as low dose (<10 mg daily), medium dose (11–15 mg daily), and high dose (>16 mg daily). A control group was selected at random and was matched with the cohort group by maternal age, gestational age, and

indication for Cesarean delivery. No differences were noted between the groups at baseline. Multiple gestation pregnancies, women with chronic pain diagnoses, and women who received opiates during the third trimester were excluded. The cohort group was continued on their prehospital dose of buprenorphine throughout their hospital stay. Analgesic requirements and VAS pain scores (0–10) were collected from both groups. Buprenorphine was not included in the daily analgesic dose totals. The mean daily buprenorphine dose was 14.6 mg (range: 4.0–32 mg). No significant difference in pain scores in the women taking buprenorphine when compared with control subjects at both 12 to 24 h (5.0 vs 4.9, $P=.47$) and 36 to 48 h (4.4 vs 4.4, $P=.47$). Women continued on buprenorphine required 14.4% more opiates in the first 48 hours postoperatively (175 vs 153 mg morphine equivalents, $P<.01$). No differences in opiate requirements were noted between the low-, medium-, and high-dose groups (195 vs 179 vs 163 mg morphine equivalents, respectively). EBP

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Is transdermal buprenorphine more effective than sustained-release tramadol for treatment of pain in adults?

EVIDENCE-BASED ANSWER

Compared with sustained-release tramadol, transdermal buprenorphine is noninferior for pain control in adults with non–cancer-related chronic pain (SOR: **B**, 2 lower quality randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2015 multicenter randomized controlled trial (RCT; n=280) compared the efficacy of transdermal buprenorphine versus sustained-release tramadol.[1] Patients were Chinese outpatient adults with a mean age of 57 years old (range from 18 to 80 years old), and 69% were female. Patients were included if they had a clinical diagnosis of nononcological moderate-to-severe musculoskeletal pain (definition of severity not provided) for four or more weeks, who had inadequate pain relief from NSAIDs and acetaminophen. Exclusion criteria included history of inadequate pain relief from any opioid analgesic, a diagnosis with cancer in the past five years, active or symptomatic heart diseases, clinically unstable respiratory disorders, mental disorders or uncontrollable seizures, and fibromyalgia pain. Patients were randomized in a 1:1 ratio to receive transdermal buprenorphine (n=141), initiated at five mcg/hour and titrated to adequate pain relief (max of 20 mcg/hour) or sustained-release tramadol tablets (n=139), initiated at 100 mg/day and titrated to adequate pain relief (max of 400 mg/day). Patients received five weeks of the analgesic dose that provided adequate pain relief, with acetaminophen available as needed (maximum 2 g/day). Pain was assessed with the visual analog scale (VAS), a patient-reported scale from 0 (no pain) to 10 (worst pain). The primary endpoint was a change in VAS pain scores from baseline, with noninferiority assumed if the treatment difference in the VAS score was within ±1.5. No significant difference in change of VAS score between the two groups was noted (buprenorphine –3.3 vs tramadol –3.8; $P=.095$). Common adverse effects in both groups included dizziness, nausea, vomiting, and constipation. This study was limited by noninferiority design and potential selection bias from exclusion of patients with suspected substance misuse.

A 2009 open-label RCT (n=135) compared the efficacy of transdermal buprenorphine and sustained-release tramadol.[2] Patients had a mean age of 64 years old, with 57% female and 99% White. Patients were included if they had a clinical and radiological diagnosis of osteoarthritis of the hip or knee, no use of high-potency opioid analgesics for greater than one week in the previous three months, and moderate-to-severe pain defined as ≥4 on an 11-point box scale (BS-11, ranging from 0 [no pain] to 10 [worst pain]). During the one-week screening phase, patients discontinued any current analgesia treatment and took four grams of acetaminophen daily. At the end of one week, patients were randomized in a 1:1 ratio to receive transdermal buprenorphine (n=69; maximum dosage of 20 mcg/hour) or sustained-release tramadol (n=66; maximum dosage of 400 mg/day), titrated as needed for adequate pain control. During the 12-week treatment phase, patients were permitted to take up to two grams of acetaminophen per day for rescue pain management. Patients recorded pain scores daily in a diary and the average weekly BS-11 score was the primary efficacy endpoint (prespecified noninferiority margin of ±1.5). The secondary efficacy endpoint was use of rescue acetaminophen as recorded by patients. No significant difference was noted in the least squares mean change in BS-11 scores from baseline to study completion between the two groups (buprenorphine –2.26 vs tramadol –2.09; *P* value not provided). No significant difference was also noted in the mean number of rescue acetaminophen tablets used (buprenorphine 206 vs tramadol, 204; *P* value not provided). The most common adverse effects in both groups included nausea, abdominal pain, chest pain, and subendocardial myocardial infarction. This study was limited by noninferiority and open-label design. EBP

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Do steroids help reduce symptoms of laryngitis (ie, vocal recovery)?

EVIDENCE-BASED ANSWER

The use of oral or inhaled steroids may aid voice recovery in people with acute laryngitis, possibly by reducing vocal fold edema (SOR: **C**, small cohort trials).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A prospective cohort study of 32 adult patients with acute dysphonia caused by laryngitis evaluated the effectiveness of treatment with inhaled fluticasone 50 mcg twice a day or oral prednisone 20 mg twice a day for seven days.[1] No control group was present in this study. Researcher excluded patients who smoked, had mental disorders, had physiological and motor problems, or had laryngeal structural disorders. Patients reported overall improvement in voice and the day their voice first improved on day 7 of treatment with a written questionnaire. Otolaryngoscopists blinded to the treatments also evaluated patients pretreatment and post-treatment with videolaryngoscopy. Of all the patients studied, 16 in the prednisone group and 15 in the fluticasone group self-reported improvement of symptoms on day 5 of treatment, but there was no difference in groups for the time to improve with the mean time being three days (*P*=.627). On videolaryngoscopy, there was a reduction in vocal cord edema with a greater ratio difference for the fluticasone treatment group compared with the prednisolone (RD –81 vs –38; *P*=.012). Videolaryngoscopy of patients in each

treatment group also demonstrated reduction in vocal cord hyperemia. The reduction of hyperemia was the same for both treatment groups (ratio difference –62; P=.10). Assessment of voice by a speech and hearing therapist also demonstrated improvement in voice quality, roughness, and breathiness (full voice assessment RD 62.5 prednisolone group vs 37.5 fluticasone group; P=.780). The study was limited by its size and lack of a control group with no steroid treatment.

A nonrandomized prospective cohort study evaluated steroid use in treatment of vocal fold edema.[2] Fifty-five adult vocal performers with vocal fold edema from overuse, allergies, or upper respiratory infections were given six days of methylprednisolone taper (24 mg starting dose, decreased by 4 mg daily). Most of the performers were lead performers in musical theater productions (n=43) with a high or moderate vocal demand (n=51). Most of the study participants completed a vocal warm up preshow (n=51), but few completed a postshow vocal cooldown or warmdown (n=16). On day 1 and day 6 of treatment, patients completed a standardized subjective assessment of their vocal performance called the Evaluation of the Ability to Sing Easily (EASE). The EASE questionnaire has a score ranging from 22 to 88 with lower scores demonstrating greater ability to sing easily at the right moment. EASE scores were divided into subscales measuring Vocal Function (VF), Pathology Risk Indicator (PRI), and Vocal Concern (VC). Videostroboscopic changes measuring amplitude and edema of the vocal folds were also used to evaluate participants pretreatment and posttreatment. On day 6 of treatment, all EASE subscale scores were significantly decreased from baseline (VF 30–21; PRI 27–17; VC 6.1–4.2, P<.0001 for each subgroup), suggesting perceived improvement in symptoms. In addition, videostroboscopic evaluation of vocal fold edema demonstrated statistically significant decrease from day 1 to day 6 from 33 to 21 (scale of 0–100, higher scores representing greater edema; mean difference –11.7, 95% CI –15.5 to –7.89). The study was limited by size, no control group, and inclusion of only vocal performers. EBP

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In patients with diabetes and periodontitis, does periodontal treatment improve glycemic control?

EVIDENCE-BASED ANSWER

Yes. Treating periodontitis by scaling and root planing (SRP) decreases HbA1C by 0.5% after 12 months in patients with diabetes (**SOR: A**, meta-analysis of RCTs). Nonsurgical periodontal therapy plus laser therapy reduces HbA1c by up to 0.28% compared with no therapy (**SOR: A**, meta-analysis of RCTs). Any combination of SRP, antibiotics, photodynamic therapy, and laser results in improvement of HbA1c up to 1.1% over four months (**SOR: B**, meta-analysis of RCTs).

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This clinical question was developed as an HDA through a standardized systemic methodology (HDA Methods, Supplemental Digital Content).

In 2022, a systematic review of 30 parallel-group RCTs (N=3,249) evaluated the effect of treating periodontitis on glycemic control in patients with diabetes mellitus (DM).[1] The trials included adult patients with DM-1 or

DM-2 (any level of control) who also had periodontal disease. Patients received either subgingival treatment or antibiotics, with or without more extensive surgical treatment, or no intervention or "usual care," including oral hygiene instruction, education, support interventions, or supragingival scaling. Patients were followed for three to 12 months. The primary outcome was the reduction in HbA1c. Periodontal treatment resulted in a reduction in HbA1c at three to four months (30 trials, N=2,443, mean difference [MD] –0.43%; 95% CI, –0.59% to –0.28%), after six months (MD –0.3%; 95% CI, –0.52% to –0.08%), and after 12 months (MD –0.5%; 95% CI, –0.55% to –0.455). Subgingival instrumentation resulted in a reduction in HbA1c of 0.46% at three to four months (20 studies, N=1,148; 95% CI, –0.64% to –0.28%), and 0.3% at six months (10 studies, N=858; 95% CI, –0.59% to –0.08%). Subgingival instrumentation and antibiotics resulted in a reduction in HbA1c of 0.48% at three to four months (11 studies, N=719; 95% CI, –0.78% to –0.17%) and 0.96% at six months (2 studies, n=85; 95% CI, –3.2% to 1.3%). Subgingival instrumentation and chlorhexidine resulted in a reduction in HbA1c of 0.21% at three to four months (3 studies, N=576; 95% CI, –0.69% to 0.28%) but not at six months. Studies that reported adverse effects generally reported little to no harm. However, adverse effects were not evaluated in most of these studies. Fourteen studies were rated overall as having high risk of bias, and double blinding was impossible due to the nature of intervention. Blinding of outcome assessment was not performed.

In 2023, a meta-analysis of 27 RCTs (N=1,611, almost all included in the above meta-analysis with the same patient population) evaluated the effect of nonsurgical periodontal therapy (NSPT) and adjuvants (antibiotics and laser therapy) on glycemic control in DM.[2] Patients received NSPT alone against no treatment or NSPT with adjuvants against NSPT alone. Compared with NSPT alone, HbA1c was reduced in patients receiving NSPT plus antibiotics (9 trials, N=872, MD –0.13%; 95% CI, –0.32% to 0.06%) and NSPT plus laser therapy (2 trials, n=77, MD –0.28%, 95% CI, –0.73% to 0.17%). Limitations included multiple studies assessed as low-quality evidence and differences in criteria to define periodontitis and treatment regimens across studies.

In 2019, a systematic review and Bayesian network meta-analysis of 14 RCTs (N=629) compared the effect of nonsurgical periodontal therapy on glycemic control of DM-2.[3] The trials included adult patients (older than 30 years) with periodontitis and DM-2. Patients were excluded from the trial if they had major complications of DM-2, periodontal treatment and antibiotic use within the previous three months, and periodontal support therapy within three months. Patients were assigned to a control group or treatment groups receiving scaling and root planing (SRP), SRP plus antibiotics, SRP plus photodynamic therapy plus doxycycline, or SRP plus laser. The primary outcomes were the mean difference in HbA1c and fasting plasma glucose at three to four months after periodontal treatment. SRP plus antibiotics (MD 0.61%; 95% CI, 0.16%–1.1%), SRP plus photodynamic therapy plus doxycycline (MD 1.1%; 95% CI, 0.11%–2.2%), SRP plus laser (MD 0.66%; 95% CI, 0.097%–1.3%), and SRP alone (MD 0.4%; 95% CI, 0.09%–0.8%) reduced HbA1c compared with no treatment. No difference was observed among the other comparisons. Researchers graded seven studies as having moderate-to-low–quality evidence, with small sample sizes and short follow-up duration as well as concerns for publication bias. EBP

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Is MRI or galactography better for diagnosing the cause of pathologic nipple discharge in women?

EVIDENCE-BASED ANSWER

Magnetic resonance imaging (MRI) is likely better. In evaluation of pathologic nipple discharge, MRI generally has higher sensitivity and specificity than galactography (SOR: **B**, meta-analysis of cohort studies and smaller conflicting cohort).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 meta-analysis of 10 retrospective and prospective cohort studies (N=921) compared the diagnostic accuracy of magnetic resonance imaging (MRI) versus galactography in women with pathologic nipple discharge (PND).[1] The mean age of patients ranged from 42 to 56 years old. Other demographic information was not provided. Both retrospective and prospective original studies were included; all other types of studies were excluded. No other information on inclusion or exclusion criteria was provided. The review provided demographic and clinical data on patients with PND, along with histologic biopsy verification or follow-up. MRI was significantly higher for sensitivity than galactography (MRI, 5 studies, N=246; 92% sensitivity; 95% CI, 85%–96% vs galactography, 4 studies; N=248; 69% sensitivity; 95% CI, 59%–78%; $P<.001$). There was also a significant difference in specificity between the two (MRI, 5 studies, N=246; 76% specificity; 95% CI, 49%–92% vs galactography, 4 studies, N=248; 39% specificity; 95% CI, 16%–69%; $P<.001$). Positive likelihood ratio (LR+) of MRI was 3.83 and negative likelihood ratio (LR–) 0.10. The LR+ of galactography was 1.13 with an LR– of 0.79. Limitations included a significant risk for publication bias in the analysis of MRI for the detection of cancers.

A 2018 single retrospective study (n=146) evaluated the diagnostic accuracy of galactography alone to diagnose pathologic nipple discharge (PND) after a negative mammogram and ultrasound.[2] The mean age of patients was 51.5 years old with a range of 17 to 93 years old from a Finnish tertiary university hospital over a nine-year period (2006–2014). Inclusion criteria were presence of PND, negative clinical breast examination as well as negative findings (for PND and cancer) on both mammogram and whole breast ultrasound; galactography was performed as a second-line investigation (n=151). MRI was performed if galactography was negative or inconclusive which occurred in 21 patients. Researcher excluded patients who had undergone mammography or ultrasound examinations after the galactography. In detection of cancerous lesions, galactography had 77.4% sensitivity, 75.7% specificity, and 76.5% overall accuracy. The LR+ of galactography was 3.19 while the LR– was 0.30. On the other hand, MRI had 85.7% sensitivity, 71.4% specificity, and 76.2% overall accuracy with LR+ of 2.99 and LR– of 0.20. EBP

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What is the most effective treatment for mild-to-moderate acne vulgaris?

EVIDENCE-BASED ANSWER

For mild-to-moderate acne, chemical peels reduce acne lesion counts by 40%, photochemical therapy by 29% to 35%, topical treatment combinations by 18% to 26%, and topical monotherapy by 11% to 18% (SOR: **A**, systematic review of randomized controlled trials). Guidelines recommend combination topical treatments (eg, benzoyl peroxide, retinoids, antibiotics) as the initial therapy for mild-to-moderate acne vulgaris (SOR: **C**, practice guidelines).

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This clinical question was developed as a HDA through a standardized systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 systematic review and network meta-analysis of 112 randomized controlled trials (RCTs) (N=20,482) evaluated the efficacy of treatments for mild-to-moderate acne vulgaris.[1] Most patients were between 12 and 45 years old with mild-to-moderate acne defined as noninflammatory lesions or 30 or fewer inflammatory lesions (on average) per patient. Interventions included topical medications (eg, benzoyl peroxide, retinoids, antiseptics, and antibiotics), oral medications (eg, antibiotics, retinoid, and contraceptives), physical treatments (eg, chemical peels, light therapies, and photochemical or photodynamic therapies), and therapy combinations of this list, which were compared with placebo. The review did not provide detailed information on dosing; most trials were between six and 24 weeks long. The review authors measured efficacy as the percent change in total acne lesion count from baseline and used a bias-adjusted model to mitigate potentially biased results due to small study size. Physical treatments, including chemical peels and photochemical therapy, had the greatest treatment efficacy compared with placebo. Topical treatment combinations were also effective compared with placebo. Overall, single topical agents were significantly less effective than combination agents (**TABLE**). Oral contraceptives initially demonstrated a small reduction in acne lesion counts, but this was not significantly different from placebo after adjusting for bias. For 60 of the 112 trials, there was some concern for bias, primarily due to unclear randomization methods, deviation from the intervention, missing outcome data, and selective reporting. Additional limitations included the moderate to very low quality of evidence, a research focus on facial acne instead of other sites, and the lack of evidence on hormone-modifying agents such as metformin and spironolactone.

A 2021 evidence-based guideline on the management of acne vulgaris from the National Institute for Health and Care Excellence recommended offering a 12-week course of a topical combination of benzoyl peroxide and clindamycin, applied once daily in the evening, for treating mild-to-moderate acne (moderate strength of recommendation, based on meta-analyses of RCTs).[2] The guideline also recommended offering a once daily topical application of either adapalene plus benzoyl peroxide or tretinoin plus clindamycin for acne of any severity (moderate strength of recommendation, based on meta-analyses of RCTs). The guideline also advised clinicians to consider topical benzoyl peroxide alone as an alternative treatment if preferred by the patient or if combination therapy was contraindicated (mild strength of recommendation, based on meta-analyses of RCTs).

A 2016 evidence-based guideline on the management of acne vulgaris from the American Academy of Dermatology recommended topical benzoyl peroxide or a topical retinoid (alone or in combination with each other), with or without a topical antibiotic, as first-line treatment for mild acne. For moderate acne, the guideline recommended a combination of topical treatments (eg, benzoyl peroxide+retinoid, benzoyl

TABLE. Treatments for mild-to-moderate acne vulgaris with a statistically significant efficacy (percent improvement in total lesion count from baseline) when compared with placebo

Treatment	No. of RCTs	No. of patients	Percent change in lesion count (95% credible interval)
Chemical peels	3	101	39.7 (12.5–66.8)
Photochemical therapy			
Combined blue/red light	3	69	35.4 (17.8–53.1)
Blue light	4	138	28.6 (12.6–44.7)
Topical combinations			
Benzoyl peroxide+retinoid	6	1,057	26.2 (16.8–35.4)
Clindamycin+retinoid	3	276	24.2 (10.8–37.5)
Macrolide+antifungal	1	74	22.8 (0.74–44.7)
Benzoyl peroxide+macrolide	2	351	20.1 (1.4–38.7)
Benzoyl peroxide+clindamycin	10	992	17.9 (8.0–27.7)
Topical monotherapy			
Retinoid	15	1,623	18.3 (10.3–26.1)
Benzoyl peroxide	15	1,109	15.6 (6.0–25.1)
Macrolide	13	765	11.7 (1.5–21.9)

Data from a network meta-analysis (with at least 50 patients per treatment) of RCTs.[1]

peroxide+antibiotic, or benzoyl peroxide+antibiotic+retinoid) or an oral antibiotic along with topical benzoyl peroxide plus a topical retinoid (A-level strength of recommendation, based on consistent and good-quality patient-oriented evidence).[3] EBP

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What are effective strategies for treating antidepressant-induced sexual dysfunction in women?

EVIDENCE-BASED ANSWER

Bupropion 150 mg twice daily as an adjunct to ongoing antidepression treatment seems to help relieve selective serotonin receptive inhibitor–induced sexual function in women without worsening psychiatric symptoms (SOR: **B**, single randomized control trial). Aerobic exercise or 50 mg once daily of Pycnogenol supplementation may also be considered as treatment options (SOR: **C**, small, open-label studies).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2013 systematic review included 23 randomized control trials (RCTs) of patients aged 16 years and older (N=1,886, with 1,103 female patients) who had sexual dysfunction secondary to treatment with selective serotonin receptive inhibitors (SSRI), serotonin/norepinephrine reuptake inhibitors (SNRI), or tricyclic antidepressants where researchers assessed the effect of pharmacologic and nonpharmacologic treatments.[1] Treatments included phosphodiesterase-5 inhibitors, bupropion, and 5-HT1A agonists compared mostly with placebo. The primary outcome was a measure of sexual function, dysfunction, and satisfaction. Several scoring systems were used such as the Female Sexual Function Index (FSFI), which includes six subscales ranging from 0 to 6 points for a total of 36 points with lower scores indicating worse sexual dysfunction. In the largest trial of female patients included in the review, the addition of bupropion 150 mg twice daily resulted in an increase in the FSFI compared with placebo (1 trial, n=213; mean difference [MD] 1.73; 95% CI, 1.41–2.05). This difference seemed to be clinically meaningful because it increased the mean total FSFI for the bupropion patients over 26, the validated cutoff point for distinguishing women with sexual dysfunction. Of the other interventions evaluated, there was no significant difference shown in the sexual function outcome. The researchers identified no data indicating a worsening of psychiatric symptoms. The limitations included inclusion of multiple interventions, multiple scales to assess the primary outcome, and absence of subgroup analysis by sex.

A 2014 RCT evaluated the effectiveness of exercise and scheduled sexual activity on improving sexual function in women taking antidepressants (n=52).[2] Patients in the study were sexually active, menstruating women, aged 18 years or older, and experiencing a change in their sexual function after starting an antidepressant (SSRI or SNRI). Patients were a median of 32 years old, predominantly white (73%), and were more likely to be treated with an SNRI (58% vs 42%). Patients completed initial intake assessments of sexual functioning, satisfaction, and psychological health before they completed a three-week baseline period where they were instructed to engage in sexual activity three times per week. Patients then entered either a three-week experimental arm, in which patients were instructed to engage in sexual activity no later than 30 minutes after completing exercise, or the control arm, where patients were instructed to engage in sexual activity no sooner than six hours after completing exercise. After completion of three weeks in the initial arm, patients were switched to the other study arm. After each arm of the study, sexual functioning was reassessed with the FSFI. In the group of patients with sexual dysfunction (n=38), overall sexual function, sexual desire, and orgasm function were significantly increased during the experimental exercise arm compared with pretrial (MD 2.41, P=.008; MD 0.75, P=.0002; MD 0.64, P=.027, respectively).This difference seemed to be clinically significant because these scores were within one standard deviation of the mean for healthy controls and more than one standard deviation from the mean of patients with sexual dysfunction disorders, per previous validation studies. Differences seen between the control and experimental exercise arms were not significant. However, the sample population was predominantly in a committed relationship (73%) and had at least some college education (93%), limiting application to a broader population. The study also had a large number of dropouts (46%).

A 2018 randomized, parallel, open-label study investigated the use of Pycnogenol, an antioxidant extract from the bark of *Pinus pinaster*, to treat sexual dysfunction in patients (N=72) taking escitalopram.[3] Patients were 70% female, mean age of 43 years, diagnosed with major depressive disorder, and stable on 10 to 20 mg of escitalopram daily for four weeks or more. The experimental group received 50 mg/day of Pycnogenol with daily escitalopram compared with the control group receiving only escitalopram daily. Sexual function was assessed by the Arizona Sexual Experiences Scale (ASEX) questionnaire consisting of five questions classifying satisfaction with desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction with scores ranging from 5 to 30 where higher scores indicate increased sexual dysfunction. A minimal clinically significant change was not defined. Symptoms were

reassessed monthly for 12 weeks. The combination treatment group experienced a statistically significant decrease in ASEX score at the end of 12 weeks compared with baseline score (15 vs 12, $P<.01$). The control group had no change in average ASEX score from baseline. There were no significant differences in ASEX scores between sexes. No adverse effects were reported. Limitations of this study included the combination group having a higher ASEX score at baseline and a lack of blinding. EBP

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Does psychoeducation added to standard cardiac rehabilitation reduce subsequent mortality or cardiovascular disease events?

EVIDENCE-BASED ANSWER

No. Patients with coronary artery disease treated with psychological interventions in addition to usual care such as cardiac rehabilitation (CR), when compared with usual care alone, do not have a significant reduction in total mortality or cardiac events (SOR: **A**, systematic review of low-quality to moderate-quality randomized controlled trials [RCTs]), although they may have a 21% reduction in cardiac mortality (SOR: **B**, systematic review of low-quality RCTs). Patients with acute coronary syndrome treated with lifestyle counseling in addition to standard CR do not demonstrate improvement in mortality or cardiac events when compared with treatment with standard CR alone (SOR: **B**, single RTC).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2017 systematic review and meta-analysis of 35 randomized controlled trials (RCTs) (N=10,703) compared the efficacy of psychological interventions (alone or with cardiac rehabilitation [CR]) versus usual care (often CR alone) in adults with a history of coronary artery disease (CAD).[1] Studies were from Europe and the United Kingdom (18 RCTs, N=5,821), the United States (12 RCTs, N=4,499), Australia (4 RCTs, N=266), and China (1 RCT, n=139). Patients were predominantly male (median 77%) with average ages ranging from 53 to 67 years old, who had a history of myocardial infarction (MI; mean 65.7%) or cardiac revascularization (mean 27.4%). The review excluded trials where 50% or more of patients had other cardiac conditions such as heart failure, atrial fibrillation, or implanted cardiac defibrillators. Psychological interventions were performed by health professionals with specific training in psychological techniques and included relaxation activities (20 RCTs), self-awareness and self-monitoring (20 RCTs), emotional support or client-led discussion (15 RCTs), and cognitive challenge or cognitive restructuring techniques (19 RCTs); patients in comparator groups did not receive psychological interventions. Patients in both intervention and comparator groups were offered usual care such as CR. Median follow-up was 12

months (range 6 months to 10.7 years). Psychological interventions did not decrease overall mortality (23 RCTs, N=7,776; relative risk [RR] 0.90; 95% CI, 0.77–1.1; moderate-quality evidence), nonfatal MI (13 RCTs, N=7,845; RR 0.82; 95% CI, 0.63–1.1; low-quality evidence), or cardiac revascularization (13 RCTs, N=6,822; RR 0.94; 95% CI, 0.81–1.1; moderate-quality evidence) compared with usual care. Psychological interventions did decrease cardiac mortality (11 RCTs, N=4,792; RR 0.79; 95% CI, 0.63–0.98); however, the evidence was deemed low-quality primarily because of small study bias. No side effects were noted of psychological interventions. Limitations included an unclear risk of bias in more than 50% of the RCTs because of concerns about the randomization methods, allocation concealment, and blinding of outcome assessment. In addition, most of the trials did not provide detailed descriptions of the intervention or the comparator.

A 2017 RCT (n=914) examined the effectiveness of adding lifestyle counseling interventions to standard CR compared with standard CR alone in patients with acute coronary syndrome.[2] Researchers recruited patients from 10 hospitals in the greater region of Rotterdam. The mean age was 57 years old, and 81% were men. All patients received standard CR defined as a 1.5-hour group exercise session conducted twice a week for the first 12 weeks of the study. The two intervention groups received either (1) standard CR with six additional face-to-face (CR+F) group sessions (3 additional group exercise sessions over the first 12 weeks and 3 additional sessions combining group exercise with behavioral counseling at 4, 6, and 12 months) or (2) standard CR with additional five to six individual telephone counseling sessions (CR+T) over nine months where specialty-trained nurses coached patients on developing a personal plan for a heart-healthy lifestyle. The control group received standard CR alone. The study reported adverse cardiac event rates at 18-month follow-up as secondary outcome measures. At 18 months, mortality in the CR+F and CR+T groups was low (0.3% in each) and was not significantly different from the mortality rate in CR-alone group (0%). Similarly, no differences were observed in rates of ST (range 0.3%–1.7%) and non-ST (range 1%–1.6%) segment elevation MI, coronary artery bypass graft surgery (range 1.7%–2.3%), or percutaneous coronary intervention (range 2.9%–4.3%) among the three groups. No side effects were noted with any interventions. Limitations included poor adherence to the study protocol, with an 18% dropout rate in the CR-alone group and 39% and 43% rates in the CR+F and CR+T groups, respectively. EBP

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Does regular physical activity improve sleep duration and quality in adults?

EVIDENCE-BASED ANSWER

Regular physical activity shows a weak-to-moderate association with improved sleep quality but not a meaningful change in sleep duration. Sleep quality and efficacy improve with general exercise (SOR: **A**, meta-analyses of randomized controlled trials [RCTs]) and high-intensity interval training (SOR: **A**, meta-analyses of RCTs). The effects from walking are inconsistent (no SOR given).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 22 RCTs (N=1,806) compared the efficacy of exercise on sleep quality (SQ) in healthy adults.[1] The analysis included studies involving

adults (>18 years old), with some studies examining men only, others women only, and some both. SQ was assessed for patients completing 2 to 12 months of physical (eg, walking) or mind–body (eg, yoga) exercises compared with a control group that did not participate in any physical or mind–body exercises. The range of exercise requirements across studies was wide: 30 to 90 minutes one to five times weekly. The meta-analysis reviewed studies using validated SQ questionnaires, including the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and Epworth Sleepiness Scale (ESS). In all subjective indices, higher scores indicated worse SQ, with ranges of 0 to 21 for the PSQI, 0 to 28 for the ISI, and 0 to 24 for the ESS. The PSQI showed improved SQ with exercise when compared with the control group (14 trials, N=1,356, MD –2.2; 95% CI, –3.0 to –1.4). Secondary study analysis found that both physical and mind–body exercise improved PSQI scores (5 physical trials, N=592; MD –2.2; 95% CI, –3.5 to –1.0; and 9 mind–body trials, N=766; MD –2.2; 95% CI, –3.2 to –1.1). Patients in the intervention groups had less severe insomnia based on ISI score (4 trials, N=313, MD –1.4; 95% CI, –2.6 to –0.41), and ESS scores showed less daytime sleepiness (2 trials, N=170; MD –2.6; 95% CI, –3.3 to –1.8). Objectively, sleep efficacy (SE), or percentage time spent sleeping while in bed, improved with intervention (6 studies, N=501; MD 1.2; 95% CI, 0.1–2.3) compared with the control. Because of self-reported indices and inability to blind participants to whether they are exercising, the risk of bias was high.

Another 2021 meta-analysis of 21 RCTs (N=755) evaluated the effect of high-intensity interval training (HIIT) on SQ compared with controls, including no intervention and other exercise regimens.[2] This review included adults 18 to 75 years old, and populations varied from athletes to cancer patients. HIIT interventions varied in timeline (1 day to 20 weeks), frequency (1 time/week to 7 times/week), and HIIT duration (8–35 minutes). HIIT programs improved SQ more than comparators based on PSQI score (8 trials, N=383; weighted mean difference [WMD] –0.90; 95% CI, –1.7 to –0.07) and ISI scores (3 trials, N=117; WMD –1.6; 95% CI, –2.4 to –0.87). A small favorable effect on SE was found with HIIT (10 trials, N=327; standardized mean difference [SMD] 0.43; 95% CI, 0.20–0.65). However, no significant effects were found with other objective measures like sleep latency (time to fall asleep after turning off lights; 6 trials, N=254; SMD 0.08; 95% CI, –0.17 to 0.33), total sleep time (9 studies, N=319; SMD 0.08; 95% CI, –0.17 to 0.33), or time in bed (4 trials, N=124; SMD –0.13; 95% CI, –0.48 to 0.23). Moderate risk of bias was noted as only 10 of the studies described the method of randomization, four used blinding of outcome measures, and two were at high risk of attrition bias.

A 2020 randomized control trial in Hungary (n=26) compared SQ and TST for university-aged adults with a four-week daily walking routine versus sedentary lifestyle.[3] The intervention was to target of 8,000 to 10,000 steps per day compared with no physical activity. Paired pre- to post-intervention results from the PSQI for individuals showed improvement in subjective SQ (mean difference 0.27; 95% CI, 0.00–0.54) but no improvement in the sleep duration score within the PSQI (mean difference 0.27; 95% CI, –0.24 to 0.77).

A 2019 randomized control trial (n=59) compared a Fitbit Zip® (step tracking device) with or without a personalized step measurement walking plan.[4] Participants were 35 years old or older (mean age 50 years old) and predominantly female (73%). A significant increase in total step count was noted in the intervention group compared with the control group (mean change from baseline 28% vs –3.6%, P=.006). No significant difference was seen in preglobal versus postglobal PSQI scores (mean 5.4 vs 5.0, P=.37) or SL (mean 6.9 vs 6.8, P=.44). EBP

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Is sports participation a protective factor in adolescent depression?

EVIDENCE-BASED ANSWER

Yes. Sports participation in adolescents and young adults is weakly negatively correlated with depression and anxiety, with the effects being more prominent for symptoms of anxiety in older adolescents and in symptoms of depression in male participants (SOR: **B**, systematic review of longitudinal and cohort studies). Participation in sports is also associated with higher levels of well-being and may be more prominent with team sports versus individual sports participation (SOR: **B**, cross-sectional study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 systematic review and meta-analysis of 29 longitudinal and cohort studies (N=122,056) explored the relationship between organized sports participation and self-reported symptoms of anxiety and depression in adolescents and young adults.[1] Participants in each study were older than eight and younger than 20 years old. Those included had to participate in sports that were "organized," and individuals engaging in non–sport-related physical activity were excluded. Multiple measures of depression were used, with the Center for Epidemiological Studies Depression Scale (CES-D) being the most common. Sports participation was defined as a competitive and organized physical activity in various settings (community-based, school-based, or competitive sport) that is played as an individual or as a team and is shaped by normative beliefs that the activity is seen as a sport. A considerable variability was observed in how sports participation was measured between the studies. The effects of sports involvement (20 studies, N=65,038) on anxiety and depression were measured using Spearman's rank correlation coefficient ("Spearman's *P*"), which is a measure designed to summarize the strength and direction of the relationship between two variables. Correlation between symptoms of depression and binary sport involvement (ie, involved or not) demonstrated a significant but weak negative mean correlation ($\rho = -0.08$; 95% CI –0.10 to –0.06). Age significantly affected this correlation, with a stronger inverse correlation between sport involvement and depression symptoms in samples of a relatively older mean age ($R^2=.39$). Binary consideration (10 studies, N=43,102) of sport involvement also revealed a small negative correlation in mean population effect ($\rho = -0.12$; 95% CI, –0.15 to –0.10) with anxiety. Male sex significantly changed this correlation ($R^2=.50$) indicating the correlation may be stronger in this group. Finally, a significant, weak, negative correlation was found between frequency of sports participation and depression symptoms ($\rho = -0.09$; 95% CI, –0.11 to –0.06). Limitations included the studies being survey-based and the significant heterogeneity among measurement of sports participation which could lead to confounding bias and measurement errors. Binary sports involvement relating to anxiety ($I^2=71\%$) and depression ($I^2=81\%$) had significant heterogeneity.

A 2020 cross-sectional study (N=5,661) examined the association between physical activity and sports participation with mental well-being and symptoms of anxiety and depression in adolescents and young adults.[2] Participants were 11 to 20 years old with a mean age of 15 years old. Data were collected through online questionnaires, and participation in sports was measured by the number of sports an individual was involved with in the last six months. This was measured as 0, 1, 2, and 3 or more sports being played. Sports were categorized by researchers as individual fitness activities or team sports. Well-being was assessed using the Warwick Edinburgh Mental Wellbeing Scale (WEMWS), which is a 14-question scale used to assess subjective well-being and psychological functioning with a minimum score of 14 and maximum score of 70. Anxiety symptoms were measured using Beck Anxiety Inventory (BAI), which is a 21-question scale used to assess the intensity of physical and cognitive symptoms of anxiety with a minimum score of 0 and maximum score of 63. Depression symptoms were measured using the Beck Depression Inventory (BDI), which is a 21-question scale used to grade depression with minimum score of 0 and maximum score of 63, with the question regarding loss of libido removed because it was deemed inappropriate for the adolescent population. Participation of male participants in sport was associated with significantly higher levels of well-being (45.9 vs 50.4, $P<.001$), lower levels of anxiety (15.5 vs 11.8, $P<.001$), and depression (10.9 vs 7.3, $P<.001$). The results in female participants were also similar to the findings shown in male participants. Limitations

included the use of self-report questionnaires that can lead to recall bias and ambiguity of interpretation. EBP

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Does smoking cessation improve mental health in adult smokers?

EVIDENCE-BASED ANSWER

Smoking cessation is associated with a small to moderate improvement in depression and anxiety scores (SOR: **B,** meta-analyses of randomized controlled trials and cohort studies) and small improvement in measures of stress, psychological quality of life, and positive affect (SOR: **B,** meta-analysis of cohort and cross-sectional studies).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 102 studies (1 randomized controlled trial [RCT], 56 secondary analyses of RCTs, and 45 cohort studies) evaluated the effect of smoking cessation on mental health in 169,500 adults.[1] Patients lived throughout the world, except Africa. Median age across studies was 45 years, with 51% male and a median use of 20 cigarettes per day. The meta-analysis compared mental health in self-identified former smokers compared with continued smokers, excluding people using just e-cigarettes. Outcomes were measured six weeks or more after baseline by various self-reported or clinical-scored measures of mental health. Each scale was converted to standardized mean difference (SMD) for comparison. Patients were followed up for six weeks to six years (median 6 months). The primary outcome included change in depression, anxiety, and mixed anxiety/depression symptoms. Between former and current smokers, there was a small to moderate decrease in depression (34 studies, N=7,156; SMD –0.3; 95% CI, –0.39 to –0.21), mixed anxiety and depression (8 studies, N=2,829; SMD –0.31; 95% CI, –0.40 to –0.22), and anxiety (15 studies, N=3,141; SMD –0.28; 95% CI,–0.43 to –0.13). There was a small decrease in stress (4 studies, N=1,792; SMD –0.19; 95% CI –0.34 to –0.01), a small improvement in psychological quality of life (19 studies, N=18,034; SMD 0.11; 95% CI 0.06–0.16), and a small improvement in positive affect (13 studies, N=4,880; SMD 0.22; 95% CI 0.11–0.33). Validity limitations included confounding bias from social, substance, and pharmacologic variables.

A 2021 meta-analysis of 49 studies (22 cross-sectional, 6 cohort, 3 randomized trials, 14 prospective trials, 1 treatment trial, 2 smoking cessation trials, and 1 unknown study type) compared the prevalence of depression in worldwide patients except Africa (N=1,948,222) who had quit smoking compared with nonsmokers and current smokers.[2] With the previous meta-analysis, eight trials overlap. Population age range was 12 to 105 years, a mix of male and female with slightly more female-predominant studies. Only four reported follow-up periods. The primary outcome was prevalence of depression in each group. Researchers assessed outcomes with various self-reported or clinician administered questionnaires. The smoking cessation population had less depression than current smokers (27 studies, N not given; odds ratio [OR] 0.63; 95% CI, 0.54–0.75), but had a more depression than never-smokers (25 studies, N not given; OR 1.2; 95% CI, 1.1–1.3). EBP

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Does using the FIFA 11+ training program reduce the incidence of injuries in soccer players?

EVIDENCE-BASED ANSWER

The FIFA 11+ training program significantly reduces the incidence of injuries in soccer players with an overall risk reduction of 47% in all injuries and a 44% risk reduction in injuries to the lower limb (SOR: **A**, meta-analysis of 4 meta-analyses). In addition, the FIFA 11+ Kids program is effective at reducing overall injury rates by 48 to 57%, initial injury rates by 57%, and lower extremity injury rates by 55% in children younger than 13 years (SOR: **A**, 2 randomized controlled trials).

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This clinical question was developed as a HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2019 meta-analysis of four meta-analyses (N=7,376), covering 15 randomized controlled trials (RCTs) and prospective cohort studies, examined the effectiveness of FIFA injury prevention programs in soccer players.[1] Demographic data were not redelineated other than all four meta-analyses included both male and female subjects. Meta-analysis studies were included if they used RCTs or prospective cohort studies examining the effectiveness of FIFA programs at preventing injury and were written in English between 1990 and 2018. Narrative reviews were excluded as were studies which did not study the complete FIFA 11+ program. Compared with control, the FIFA 11+ injury prevention program significantly reduced the risk of all injuries (4 studies, N=13,737; risk ratio [RR] 0.53; 95% CI, 0.50–0.57; I^2=34%) and lower limb injuries (2 studies, N=6,869; RR 0.56; 95% CI, 0.49–0.64; I^2=52%). Limitations included that primary studies often appeared in more than one meta-analysis allowing for the overrepresentation of some studies. In addition, two of the included meta-analyses were of low methodological quality.

A 2023 clustered RCT (n=780) compared injury rates between teams using usual warm-ups versus teams using the FIFA 11+ Kids injury prevention program over the course of one season.[2] Patients were male soccer players between seven and 13 years old who were registered to a local soccer association in Saudi Arabia. Patients were excluded if they had upper or lower limb injuries requiring medical attention within the past six months or any systemic diseases, fractures, or surgery in the last year. Patients were randomized to the experimental arm (n=391) using the FIFA11+ Kids program for 15 to 20 min twice per week, or the control normal warm-ups (n=389). The primary outcomes included incidence of overall, initial, and recurrent injuries per 1,000 player, and time loss in days. The mechanism of injury was categorized as contact, noncontact, or overuse (definition of each category not provided). Compared with the control group, the intervention group experienced 57% fewer injuries overall (intervention, 0.85 injuries/1,000 exposure hours vs control, 2.01 injuries/1,000 h; risk ratio [RR] 0.43; 95% CI, 0.29–0.61) and also a significant reduction of initial injuries by 57% (intervention, 0.82 injuries/1,000 h vs control, 1.9 injuries/1,000 h; RR 0.43; 95% CI, 0.30–0.63). There was no effect on incidence of recurrent injury or injury severity. Limitations included that hours spent in physical activities outside of the team were not considered.

A 2018 multinational cluster RCT (n=3,895) assessed the efficacy of FIFA 11+ Kids in preventing injuries in soccer players younger than 13 years.[3] This study was not included in the 2019 meta-analysis

above. Patients were club soccer players between seven and 12 years from Switzerland, Germany, the Czech Republic, and the Netherlands. Patients were excluded if they already used a warm-up focused on neuromuscular control. Patients were randomized to either warm-up as usual (n=1,829) or the FIFA 11+ Kids program (n=2,066). It should be noted that the FIFA11+ Kids program contained some different elements than the basic FIFA 11+, which addressed developmental and age-appropriate motor skills. The primary outcome was the overall risk of injuries. Compared with the control group, the overall injury rate in the intervention group was reduced by 48% (hazard ratio [HR] 0.52; 95% CI, 0.32−0.86). Injuries requiring greater than 28 days off (HR 0.26; 95% CI 0.10−0.64) and lower extremity injuries (HR 0.45; 95% CI, 0.24–0.84) were also significantly lower in the intervention group. Limitations included a lower proportion of girls and difficulty in blinding participants. EBP

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In pregnant women with a history of depression, does the use of a selective norepinephrine reuptake inhibitor during pregnancy increase the risk of congenital malformation compared with a selective serotonin reuptake inhibitor?

EVIDENCE-BASED ANSWER

Probably not. There is no difference in overall rates of congenital malformations with first trimester exposure to serotonin norepinephrine reuptake inhibitors (SNRIs) compared with SSRIs (SOR: **B**, meta-analysis of cohort studies). SNRI and SSRI exposure is associated with an increased risk of cardiac malformation compared with no exposure (SOR: **B**, meta-analysis of cohort studies).

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This clinical question was developed as a HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 meta-analysis of eight cohort studies (N=6,972,503) analyzed the association between serotonin norepinephrine reuptake inhibitor (SNRI) use and the incidence of congenital malformations.[1] The analysis included SNRI exposure (venlafaxine, duloxetine, and others not specified; dosing not provided) in the first trimester of pregnancy.

This analysis excluded studies that did not have a control group. Risk of SNRI exposure during the first trimester was compared with no exposure to antidepressant therapy, exposure to selective serotonin reuptake inhibitors (SSRIs), and no medication exposure in patients with a clinical indication for antidepressants. Individual SSRIs included in this study were not detailed. The primary outcome was the association between overall congenital malformation rate and SNRI exposure with secondary outcomes of specific type of malformation. There was no difference in rates of congenital malformation with first trimester exposure of SNRIs compared with SSRIs (4 studies, N=97,673; risk ratio [RR] 1.1; 95% CI; 0.97–1.3). SNRIs taken in the first trimester were not associated with an increased risk of congenital malformation compared with no SNRI exposure (5 trials, N=5,635,072; RR 1.1; 95% CI, 0.94–1.2). For secondary outcomes, there was an increased risk of cardiac malformations in patients exposed to all SNRIs compared with no antidepressant exposure (5 studies, N=6,879,533; RR 1.3; 95% CI, 1.2–1.5). However, there was no difference in cardiac malformations specifically with venlafaxine alone or duloxetine alone compared with no exposure. Limitations included the lack of studies on system-specific malformations.

A 2021 meta-analysis of 20 cohort and case–control studies (N=5,337,223) evaluated individual antidepressants for congenital heart malformation.[2] There are four studies overlapping with the prior meta-analysis. This analysis included SSRIs (sertraline, fluoxetine, paroxetine, escitalopram, and citalopram), SNRIs (duloxetine and venlafaxine), bupropion, and tricyclic antidepressants. Dosing and duration of any medications were not specified. This review included patients (15 years old or older) exposed to any antidepressant in the first trimester of pregnancy and excluded studies with abortive, mortal, or neurobehavioral outcomes. Pregnant patients without exposure to antidepressants served as the comparison. The primary outcome was any association of antidepressant exposure with congenital heart defects. There was an increased risk of congenital heart defects with first trimester exposure to either SSRIs (16 trials, N=4,153,354; odds ratio [OR] 1.3; 95% CI, 1.2–1.4) or SNRIs (4 trials, N=2,310,708; 1.7; 95% CI, 1.4–2.1) as compared with no exposure. Compared with no exposure, there specifically was a higher incidence of congenital heart defects with fluoxetine (8 trials, N=3,766,838; OR 1.4; 95% CI, 1.1–1.7), paroxetine (9 trials, N=3,811,893; OR 1.6; 95% CI, 1.3–2.0), and sertraline (7 trials, N=3,751,879; OR 1.3; 95% CI, 1.1–1.5) but not with citalopram, escitalopram, or venlafaxine. Limitations included uncertainty of patient adherence to antidepressant medications. EBP

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Is ketamine effective for treatment-resistant depression?

EVIDENCE-BASED ANSWER

Intravenous (IV) ketamine at 0.5 mg/kg given as a single or multiple doses moderately improves depression scores, clinical response, and remission rates in adults with treatment-resistant depression (TRD) when compared with placebo, but safety and efficacy data beyond seven days after treatment are lacking (SOR: **A**, meta-analysis of randomized control trials [RCTs]). Intranasal esketamine, used adjunctively to other antidepressants, is slightly more effective than placebo at decreasing depression severity and improving response and remission in adults with major depressive disorder who are treatment-resistant or acutely suicidal (SOR: **A**, meta-analysis of RCTs).

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systematic review and meta-analysis of 28 clinical trials (not limited to randomized control trials [RCTs], N=1,000) evaluated the effect of ketamine infusion in patients presenting with treatment-resistant depression (TRD).[1] Only studies published in English or French were included. Patients were adults 18 years old or older, diagnosed with major depressive disorder or bipolar disorder who also met criteria for TRD, generally defined as failing two or more treatment modalities. Concurrent antidepressant medication usage was not restricted; 13 studies required medication washouts before ketamine treatment. Included studies treated patients with intravenous (IV) ketamine 0.5 mg/kg per dose, some studies using one and others using multiple doses. Researchers excluded studies in which patients were diagnosed with secondary depression or were using ketamine as adjunctive treatment for other disorders. Primary outcomes included depression scores (measured using various clinician-rated or self-reported measures which were not listed in this meta-analysis) and clinical response (a reduction of at least 50% in depression scores) from baseline 24 h or seven days after treatment. Secondary outcomes included rates of remission, defined as an absence of depression as measured by clinician-rated or self-reported depression measurements. In placebo-controlled RCTs, depression scores improved moderately in the ketamine treatment group relative to placebo (7 studies, N=578; standardized mean difference [SMD] 0.68; 95% CI, 0.46–0.90; $P<.0001$). In these same seven studies, clinical response was also superior in the ketamine group (odds ratio [OR] 6.3; 95% CI, 3.3–12; $P<.0001$). Remission rates were higher in patients treated with IV ketamine compared with placebo (4 studies, N=410; OR=5.11; 95% CI, 2.2–12; $P<.003$). None of the studies in this meta-analysis looked at data past seven days, thus limiting any interpretation of long-term safety or efficacy outcomes.

A 2020 meta-analysis of five RCTs (N=774) evaluated the efficacy of adjunctive intranasal esketamine compared with intranasal placebo in MDD.[2] Studies included double-blinded RCTs of adults (mean age not reported) using intranasal esketamine as an adjunct to other antidepressants. Patients all suffered from MDD and had either been diagnosed with TRD (n=708) or were acutely suicidal (n=66). Treatments included intranasal esketamine 28 mg, 56 mg, or 84 mg twice weekly over two to four weeks. Depression severity was measured using the Montgomery–Asberg Depression Rating Scale (MADRS), a 10-item clinician-administered scale scored from 0 to 60 with higher scores indicative of worse depression. This analysis excluded patients with bipolar disorder, dysthymic disorder, psychotic features, minor depressive disorder, seasonal affective disorder, medical comorbidities, or alcohol or substance abuse disorders. Primary outcome was change in depression scores between adjunctive esketamine and placebo measured at baseline and end of treatment period. Secondary outcomes evaluated the rates of response (criteria not described in publication) and remission (MADRS less than or equal to 10 [1 study] or 12 [4 studies]). Adjunctive esketamine was more effective than placebo at reducing depression scores (SMD=0.36; 95% CI; 0.24–0.49, $P<.0001$). Rates of response (RR 1.40; 95% CI, 1.2–1.6; $P<.0001$) and remission (RR 1.45; 95% CI, 1.2–1.8; $P<.0001$) were also superior in the intranasal esketamine group. Limitations included varying definitions of TRD across pooled studies and use of esketamine only as an adjunct. EBP

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Does regular ingestion of whole cranberries, cranberry juice, or products containing these as whole ingredients prevent recurrent urinary tract infections in women?

EVIDENCE-BASED ANSWER

Yes. In women at risk for recurrent urinary tract infections (UTIs), consuming products containing whole cranberry lowers risk of another UTI event by up to 32% (SOR: **A**, meta-analysis of randomized controlled trials).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021 meta-analysis of 28 randomized controlled trials (RCTs; N=3,979) examined the effectiveness of cranberry-containing products on preventing urinary tract infections (UTIs) in susceptible populations compared with placebo.[1] The authors defined "susceptible populations" as patients with recurrent UTIs (not defined in the meta-analysis), pregnant people, children, older adults, and patients with indwelling catheters or neuropathic bladders. Studies varied in their definition of UTI occurrence; for most studies, bacteriuria of >100,000 colony-forming units (CFUs) with symptoms (undefined) qualified as a UTI incident. Nine studies also included pyuria in their definition. Authors used the Cochrane Risk of Bias tool to evaluate the quality of included studies and used trial sequential analysis to control for type I and type II errors in the meta-analysis. Overall, cranberry therapy resulted in a 30% risk reduction in UTI events for susceptible patients (relative risk [RR] 0.7; 95% CI, 0.56–0.83). A subgroup analysis showed that women with recurrent UTIs had a 32% reduction in developing a subsequent UTI (8 studies, N=1,343; RR 0.68; 95% CI, 0.56–0.81) compared with placebo. Studies that specified use of only cranberry juice showed a similar reduction in UTI events (13 studies, N=2,125; RR 0.65; 95% CI, 0.54–0.77). This study had several limitations that included a high degree of heterogeneity in type of cranberry product (eg, juice, capsule) and patient populations. Also, adherence to study protocols was primarily patient reported, and some studies used a threshold of 1,000 CFUs to define UTI, which is much lower than the standard of care.

A 2021 single-center RCT (n=55) evaluated the effectiveness of a capsule containing *Lactobacillus paracasei*, concentrated cranberry juice, and D-mannose in the prevention of recurrent urinary tract infections (UTIs).[2] Patients were premenopausal women 18 to 50 years old (mean age 39.3 years old), diagnosed with an acute UTI, and had a history of recurrent uncomplicated UTIs. The authors defined "recurrence" as three or more documented UTI episodes in the past year or two in the last six months. The primary outcome was rate of UTI recurrence during the entire 150-day study period. The secondary outcome was the proportion of participants who remained UTI-free through the entire study, labeled "responders." A diagnosis of UTI was based on a urine culture with ≥1,000 CFUs of a urinary pathogen and at least two of the following symptoms: dysuria, nocturia, urgency, frequency, suprapubic pain, or hematuria. Participants received fosfomycin 3 g once daily for two days to treat the underlying infection. After infection resolved (no symptoms, <1,000 CFUs in urine culture), patients were assigned randomly to one of three groups. Group 1 received the intervention capsules once daily for 10 days out of each month for 90 days, group 2 received the intervention capsules once daily every day for 90 days, and group 3 received no further treatment. Patients attended three visits during the study: inclusion on day 0, at the end of treatment at day 90, and a final visit at the end of the study period

(day 150). If a patient developed UTI symptoms during the study period, infection was confirmed with a urine culture. If positive, prophylaxis was stopped and they received another two days of fosfomycin therapy. Patients with a single UTI recurrence restarted prophylaxis, but if a second infection occurred, they did not continue the study. The total number of UTI episodes was greater in the control group (group 3) compared with group 1 or group 2 (52.9% vs 16% and 15.5%, respectively; $P<.01$). The two intervention groups did not differ significantly in proportion of responders (65.8% vs 68.7%, $P>.05$). No adverse events were reported with this treatment. Limitations included lack of blinding and short duration of follow-up. EBP

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Is triptan therapy a safe option for acute migraine in pregnancy?

EVIDENCE-BASED ANSWER

Triptan therapy during pregnancy is not associated with significant differences in congenital malformations, low birth weight, or preterm delivery (strength of recommendation [SOR]: **B**, meta-analysis of cohort studies). There may be a slight increase in atonic uterus (number needed to harm [NNH]=53), greater than 500 mL blood loss (NNH=29), and spontaneous abortion (NNH=244). No increased risk of ADHD in offspring with triptan use in pregnancy was noted (SOR: **B**, cohort studies).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systematic review and meta-analysis of six cohort studies investigated the prevalence of pregnancy outcomes in migraine-treated patients (N=6,879).[1] The review included exposure to pharmacological treatments for migraines (including triptans) at some point during their pregnancy based on prescription monitoring and telephone interview data. Given limited data, relative risk meta-analyses were only conducted from three of the studies. Compared with the general population, triptans did not significantly increase the risk of major malformations (2 studies; N=1,897; odds ratio [OR] 1.1; 95% CI, 0.83–1.4), low birth weight (2 studies; N=1,499; OR 1.2; 95% CI, 0.94–1.5), or preterm birth (2 studies, N=1,499; OR 1.5; 95% CI, 0.37–6.1). A major limitation to this study was that frequency and timing of exposure to triptans including in relation to trimester of pregnancy was not consistent or specified. A significant heterogeneity was present, and it was unclear if triptans before pregnancy were included in the meta-analysis.

A 2010 prospective Norwegian cohort study reviewed a registry of 69,929 pregnant women and their newborns and compared pregnant women who were exposed to triptans during pregnancy (n=1,535) with those who were only exposed to triptans six months before pregnancy (N=373) and pregnant women who never used triptans (N=68,021) from 1999 to 2007.[2] The cohort study did separate exposures by trimester. Two questionnaires were given to

women, one during the first 18 weeks and the other at gestational week 30. Delivery information was also reviewed. After adjusting for confounders, this study found that in those with triptan exposure in the third trimester, a slight increase in atonic uterus (OR 1.4; 95% CI, 1.1–1.8; number needed to harm [NNH]=53) and greater than 500 ml blood loss (OR 1.3; 95% CI, 1.1–1.5; NNH=29) was noted. This study was limited by multiple confounding factors with the triptan-exposed group having increased medical complications such as obesity and pre-eclampsia, along with more frequent exposure to other medications such as NSAIDS. Triptan exposure was not quantified in this study.

In a 2021 population-based cohort study from Quebec analyzing 233,900 eligible singleton pregnancies from 1998 to 2015 that resulted in live birth, triptan use was compared with control on the pregnancy outcomes of prematurity, low birth weight, and major congenital malformations.[3] In this cohort, 526 patients (0.22%) were exposed to triptans. No statistically significant difference was noted in the rates of prematurity (relative risk [RR] 1.3; 95% CI, 0.99–1.7), low birth weight (RR 1.2; 95% CI, 0.83–1.6), or major congenital malformations (RR 1.0; 95% CI, 0.79–1.4). The risk of spontaneous abortion was analyzed using a nested case–control design within the cohort to compare 29,104 spontaneous abortion cases with 287,607 controls and rates of triptan use. Spontaneous abortion rates in patients who used triptans were significantly higher at 0.66 (n=192) versus 0.25 (n=713) in the control group, with an adjusted odds ratio [aOR] of 1.6 (95% CI, 1.3–2.0; NNH=244). Rates of triptan use were based on filling of prescription from the pharmacy.

A 2022 follow-up cohort study using the 2010 Norwegian data assessed the risk of ADHD with maternal triptan use by reviewing information from the previous questionnaires.[4] A follow-up questionnaire was conducted when the child reached age five years old and then was followed for a mean of 11 years. Only singleton pregnancies whose mothers completed the final questionnaire were included in the study (n=10,167). No increased risk of ADHD diagnosis was noted (hazard ratio [HR] 1.2; 95% CI, 0.78–1.7) compared with unexposed groups. No differences were noted in ADHD symptom scores based on the Conner's Parental Rating Scale, performed at five years old between groups exposed to triptans during pregnancy versus unexposed (weighted mean difference –0.11; 95% CI, –0.25 to 0.04). A limitation of this study was the inability to break down exposure by trimester. EBP

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What are the effective medication treatments of leg cramps in pregnancy?

EVIDENCE-BASED ANSWER

There are insufficient data to strongly recommend any medication for leg cramps in pregnancy. Oral magnesium may reduce the frequency of leg cramps in pregnancy and promote the resolution of symptoms (SOR: **B**, meta-analyses of randomized controlled trials (RCTs) with inconsistent results). Calcium and B vitamins may also have benefit (SOR: **B**, systematic review of RCTs).

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This clinical question was developed as a HDA through a standardized systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systemic review including eight randomized controlled trials (RCTs) (N=576) examined the efficacy and side effects of several medications for leg cramps in pregnancy, with a primary outcome of frequency of leg cramps.[1] Patients ranged from 14 to 36 weeks of gestation and received medication for two to four weeks. Oral magnesium was more likely to lead to the resolution of symptoms than placebo (1 trial, n=69, relative risk [RR] 5.7; CI 1.4–24) and to decrease frequency of symptoms by 50% (1 trial, n=86, RR 1.4; CI 1.1–1.9) but did not decrease pain score on a scale from 0 to 4 (1 trial, n=38, mean difference [MD] 1.8; CI –1.3 to 4.9). Magnesium studies were too heterogeneous to pool outcomes data, and no two studies used the same dose or frequency. Calcium also demonstrated improved symptom resolution compared with placebo (1 trial, n=43, RR 8.6; CI 1.2–62) and decreased frequency of cramps over a two-week period (1 study, n=60, MD –0.5, CI –0.7 to –0.3). There was improvement in a composite outcome of frequency/intensity for B vitamins (1 study, n=42, RR 0.2, CI 0.1–0.7). Vitamin C, vitamin D, and combined calcium–vitamin D did not significantly impact leg cramps. None of the medications studied had significant side effects.

A 2021 meta-analysis of four RCTs (n=332) studied leg cramps in pregnant women on oral magnesium and included one new study published after the systemic review.[2] Of note, unlike the systemic review, this meta-analysis pooled data from all four studies. Treatment involved oral magnesium 300 to 360 mg daily over two to four weeks, and outcomes included cramping frequency, symptom resolution, and side effects. Included patients were pregnant women with singleton pregnancies in multiple countries diagnosed with leg cramps, 12 to 36 weeks of gestation, not on hemodialysis, and without restless leg syndrome. The meta-analysis found no effect of oral magnesium on the frequency of leg cramps (weighted mean difference [WMD] –0.47; 95% CI, –1.1 to 0.20) or resolution of leg cramps (OR 0.47; 95% CI, 0.14–1.5) compared with placebo. Magnesium also had no significant side effects compared with placebo (OR 1.8; 95% CI, 0.90–3.7). EBP

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What are the benefits and harms of statin treatment for familial hypercholesterolemia in children/adolescents?

EVIDENCE-BASED ANSWER

Statin treatment in children with familial hypercholesterolemia results in significant reduction in total cholesterol and LDL. No evidence of liver dysfunction, myopathy, or rhabdomyolysis is present (SOR: **A**, systematic review of randomized controlled trials). Statin therapy in these children is also associated with a lower incidence of cardiovascular events and death from cardiovascular causes (SOR: **B.** cohort study).

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This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 meta-analysis of nine double-blinded randomized controlled trials (RCTs) (N=1,177) evaluated the efficacy and safety of statin treatments compared with placebo over 12 to 104 weeks.[1] It included patients six to 18 years old diagnosed with familial hypercholesterolemia (FH) diagnosed clinically or with DNA confirmation. Clinical criteria included elevated serum lipid levels, positive family history of early cardiovascular disease or FH, and manifested certain standards for sexual development. It excluded children with any concomitant diseases who elevated lipid levels or medications that interacted with statins. The primary outcomes included change in carotid intima-media thickness, serum low-density lipoprotein (LDL) cholesterol level, and measures of growth and maturation. Statin therapy significantly reduced both mean LDL cholesterol (6 studies, N=669; mean difference [MD] –32 mg/dL; 95% CI, –35 to –29 mg/dL; I^2=89%) and total cholesterol (6 studies, N=669; MD –27 mg/dL; 95% CI –29 to –26 mg/dL; I^2=88%) at the end of a one-year follow-up period. No difference was observed in puberty based on acceleration of tanner staging at two years (1 study; n=211; relative risk 0.95; 95% CI, 0.77–1.2). No evidence of liver dysfunction, myopathy, or rhabdomyolysis was present compared with placebo. The confidence intervals of pooled results were either wide or not able to be estimated due to very low number of events. Key limitations of the studies examined included an overall short study duration in addition to limited long-term follow-up for further assessment.

A retrospective cohort study in 2019 did a 20-year follow-up of 214 children with familial hypercholesterolemia (FH) to determine cardiovascular outcomes between patients treated with pravastatin and placebo.[2] Children in the intervention group at the time who were below 14 years old were given 20 mg of pravastatin once nightly while those 14 years old and older were given 40 mg of pravastatin once nightly. The group had a patient population of 47% male with a mean age of 13 years old. All patients had a parent with confirmed FH, and most had a genetic LDL receptor mutation. Unaffected siblings (n=95) served as a control group. The follow-up was performed through a hospital visit or telephone interview and used a questionnaire to document medical history, lifestyle habits, and medication use. Serum lipid markers, carotid intima-media thickness as well as history of cardiovascular events, and deaths were compared. The mean LDL cholesterol at baseline was 237 mg/dL compared with 99 mg/dL in controls (n=214; difference 139; 95% CI, 131–147). At the follow-up, the LDL cholesterol was 161 mg/dL versus 122 mg/dL in the controls (n=184; MD 39 mg/dL; 95% CI, 26–52). The treatment group has a mean decrease of 32% in LDL cholesterol level at the 20-year follow-up, and 20% of them achieved the treatment goal of LDL <100 mg/dL. Both patients and their unaffected siblings showed similar mean progression of carotid intima-media thickness based on ultrasound. Using the Kaplan-Meier survival curves, patients when compared with their parents showed a lower cumulative incidence of cardiovascular events (1% vs 26%) and death from cardiovascular causes (0% vs 7%) before age 40 years.. Key limitations of the study included its observational nature as well as other changes and improvement in health care over time affecting its results. EBP

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